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Patentanmeldung Nr. Patent application No. Demande de brevet n°

98203148.6

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Der Präsident des Europäischen Patentamts;
Im Auftrag

For the President of the European Patent Office

Le Président de l'Office européen des brevets
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Sheet 2 of the certificate
Page 2 de l'attestation

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See for original title of the application page 1 of the description

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18. 09. 1998

IL-5 INHIBITING 6-AZAUURACIL DERIVATIVES

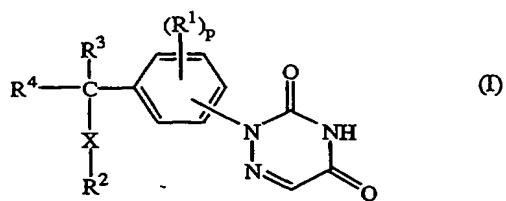
5 The present invention concerns IL-5 inhibiting 6-azauracil derivatives useful for treating eosinophil-dependent inflammatory diseases; to processes for their preparation and compositions comprising them. It further relates to their use as a medicine.

10 Eosinophil influx, leading to subsequent tissue damage, is an important pathogenic event in bronchial asthma and allergic diseases. The cytokine interleukin-5 (IL-5), produced mainly by T lymphocytes as a glycoprotein, induces the differentiation of eosinophils in bone marrow and, primes eosinophils for activation in peripheral blood and sustains their survival in tissues. As such, IL-5 plays a critical role in the process of eosinophilic inflammation. Hence, the possibility that inhibitors of IL-5 production would reduce the production, activation and/or survival of eosinophils provides a therapeutic approach to the treatment of 15 bronchial asthma and allergic diseases such as, atopic dermatitis, allergic rhinitis, allergic conjunctivitis, and also other eosinophil-dependent inflammatory diseases.

20 Steroids, which strongly inhibit IL-5 production *in vitro*, have long been used as the only drugs with remarkable efficacy for bronchial asthma and atopic dermatitis, but they cause various serious adverse reactions such as diabetes, hypertension and cataracts. Therefore, it would be desirable to find non-steroidal compounds having the ability to inhibit IL-5 25 production in human T-cells and which have little or no adverse reactions.

25 US 4,631,278 discloses α -aryl-4-(4,5-dihydro-3,5-dioxo-1,2,4-triazin-2(3H)-yl)benzene-acetonitriles and US 4,767,760 discloses 2-(substituted phenyl)-1,2,4-triazine-3,5(2H,4H)-diones, all having anti-protozoal activity, in particular, anti-coccidial activity. EP 831,088 discloses 1,2,4-triazine-3,5-diones as anticoccidial agents. Unexpectedly, the 6-azauracil derivatives of the present invention prove to be potent inhibitors of the 30 production of IL-5.

The present invention is concerned with the compounds of formula



the *N*-oxides, the pharmaceutically acceptable addition salts and the stereochemically isomeric forms thereof, wherein :

35 p represents an integer being 0, 1, 2, 3 or 4;

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X represents O, S, NR⁵ or a direct bond;

Y represents O, S, NR⁵, or S(O)₂;

each R¹ independently represents C₁₋₆alkyl, halo, polyhaloC₁₋₆alkyl, hydroxy, mercapto, C₁₋₆alkyloxy, C₁₋₆alkylthio, C₁₋₆alkylcarbonyloxy, aryl, cyano, nitro, Het³, R⁶, NR⁷R⁸ or C₁₋₄alkyl substituted with Het³, R⁶ or NR⁷R⁸;

R² represents Het¹, C₃₋₇cycloalkyl, C₁₋₆alkyl or C₁₋₆alkyl substituted with one or two substituents selected from hydroxy, cyano, amino, mono- or di(C₁₋₄alkyl)amino, C₁₋₆alkyloxy, C₁₋₆alkylsulfonyloxy, C₁₋₆alkyloxycarbonyl, C₃₋₇cycloalkyl, aryl, aryloxy, arylthio, Het¹, Het¹oxy and Het¹thio; and if X is O, S or NR⁵, then R² may also represent aminocarbonyl, aminothiocarbonyl, C₁₋₄alkylcarbonyl, C₁₋₄alkylthiocarbonyl, arylcarbonyl, arylthiocarbonyl, Het¹carbonyl or Het¹thiocarbonyl;

R³ represents hydrogen, C₁₋₆alkyl or C₃₋₇cycloalkyl;

R⁴ represents hydrogen, C₁₋₆alkyl or C₃₋₇cycloalkyl; or

R³ and R⁴ taken together form a C₂₋₆alkanediyl;

R⁵ represents hydrogen or C₁₋₄alkyl;

each R⁶ independently represents C₁₋₆alkylsulfonyl, aminosulfonyl, mono- or di(C₁₋₄alkyl)-aminosulfonyl, mono- or di(benzyl)aminosulfonyl, polyhaloC₁₋₆alkylsulfonyl, C₁₋₆alkylsulfinyl, phenylC₁₋₄alkylsulfonyl, piperazinylsulfonyl, aminopiperidinylsulfonyl, piperidinylaminosulfonyl, N-C₁₋₄alkyl-N-piperidinylaminosulfonyl or mono- or di(C₁₋₄alkyl)aminoC₁₋₄alkylsulfonyl;

each R⁷ and each R⁸ are independently selected from hydrogen, C₁₋₄alkyl, hydroxyC₁₋₄alkyl, dihydroxyC₁₋₄alkyl, aryl, arylC₁₋₄alkyl, C₁₋₄alkyloxyC₁₋₄alkyl, C₁₋₄alkylcarbonyl, aminocarbonyl, arylcarbonyl, Het³carbonyl, C₁₋₄alkylcarbonyloxy-C₁₋₄alkylcarbonyl, hydroxyC₁₋₄alkylcarbonyl, C₁₋₄alkyloxycarbonylcarbonyl, mono- or di(C₁₋₄alkyl)aminoC₁₋₄alkyl, arylaminocarbonyl, arylaminothiocarbonyl, Het³aminocarbonyl, Het³aminothiocarbonyl, C₃₋₇cycloalkyl, pyridinylC₁₋₄alkyl, C₁₋₄alkanediyl-C(=O)-O-R¹⁴, -C(=O)-O-R¹⁴, -Y-C₁₋₄alkanediyl-C(=O)-O-R¹⁴, Het³ and R⁶;

R⁹ and R¹⁰ are each independently selected from hydrogen, C₁₋₄alkyl, hydroxyC₁₋₄alkyl, dihydroxyC₁₋₄alkyl, phenyl, phenylC₁₋₄alkyl, C₁₋₄alkyloxyC₁₋₄alkyl, C₁₋₄alkylcarbonyl, aminocarbonyl, phenylcarbonyl, Het³carbonyl, C₁₋₄alkylcarbonyloxyC₁₋₄alkylcarbonyl, hydroxyC₁₋₄alkylcarbonyl, C₁₋₄alkyloxycarbonylcarbonyl, mono- or di(C₁₋₄alkyl)aminoC₁₋₄alkyl, phenylaminocarbonyl, phenylaminothiocarbonyl, Het³aminocarbonyl, Het³aminothiocarbonyl, C₃₋₇cycloalkyl, pyridinylC₁₋₄alkyl, C₁₋₄alkanediyl-C(=O)-O-R¹⁴, -C(=O)-O-R¹⁴, -Y-C₁₋₄alkanediyl-C(=O)-O-R¹⁴, Het³ and R⁶;

each R¹¹ independently being selected from hydroxy, mercapto, cyano, nitro, halo, trihalomethyl, C₁₋₄alkyloxy, formyl, trihaloC₁₋₄alkylsulfonyloxy, R⁶, NR⁷R⁸, C(=O)NR⁷R⁸, -C(=O)-O-R¹⁴, -Y-C₁₋₄alkanediyl-C(=O)-O-R¹⁴, aryl, aryloxy,

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arylcarbonyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkyloxy, phthalimide-2-yl, Het³, Het⁴ and $C(=O)Het^3$;

R¹² and R¹³ are each independently selected from hydrogen, C_{1-4} alkyl, hydroxy C_{1-4} alkyl, dihydroxy C_{1-4} alkyl, phenyl, phenyl C_{1-4} alkyl, C_{1-4} alkyloxy C_{1-4} alkyl, C_{1-4} alkylcarbonyl, phenylcarbonyl, C_{1-4} alkylcarbonyloxy C_{1-4} alkylcarbonyl, hydroxy C_{1-4} alkylcarbonyl, C_{1-4} alkyloxycarbonylcarbonyl, mono- or di(C_{1-4} alkyl)amino C_{1-4} alkyl, phenylamino-carbonyl, phenylaminothiocarbonyl, C_{3-7} cycloalkyl, pyridinyl C_{1-4} alkyl, C_{1-4} alkanediyl- $C(=O)$ -O-R¹⁴, - $C(=O)$ -O-R¹⁴, -Y- C_{1-4} alkanediyl- $C(=O)$ -O-R¹⁴ and R⁶;

each R¹⁴ independently represents hydrogen, C_{1-4} alkyl, C_{3-7} cycloalkyl,

10 aminocarbonylmethylene or mono- or di(C_{1-4} alkyl)aminocarbonylmethylene;

aryl represents phenyl optionally substituted with one, two or three substituents each independently selected from nitro, azido, cyano, halo, hydroxy, C_{1-4} alkyl, C_{3-7} cycloalkyl, C_{1-4} alkyloxy, formyl, polyhalo C_{1-4} alkyl, NR⁹R¹⁰, $C(=O)NR^9R^{10}$, $C(=O)$ -O-R¹⁴, R⁶, -O-R⁶, phenyl, Het³, $C(=O)Het^3$ and C_{1-4} alkyl substituted with hydroxy, C_{1-4} alkyloxy, $C(=O)$ -O-R¹⁴, -Y- C_{1-4} alkanediyl- $C(=O)$ -O-R¹⁴, Het³ or NR⁹R¹⁰;

15 Het¹ represents a heterocycle selected from pyrrolyl, pyrrolinyl, imidazolyl, imidazolinyl, pyrazolyl, pyrazolinyl, triazolyl, tetrazolyl, furanyl, tetrahydrofuranyl, thienyl, thiolanyl, dioxolanyl, oxazolyl, oxazolinyl, isoxazolyl, thiazolyl, thiazolinyl, isothiazolyl, thiadiazolyl, oxadiazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyranyl, pyridazinyl,

20 pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl, dioxanyl, dithianyl, trithianyl, triazinyl, benzothienyl, isobenzothienyl, benzofuranyl, isobenzofuranyl, benzothiazolyl, benzoxazolyl, indolyl, isoindolyl, indolinyl, purinyl, 1*H*-pyrazolo[3,4-d]pyrimidinyl, benzimidazolyl, quinolyl, isoquinolyl, cinnolinyl, phtalazinyl, quinazolinyl, quinoxalinyl, thiazolopyridinyl, oxazolopyridinyl and imidazo[2,1-b]thiazolyl; wherein said heterocycles each independently may optionally be substituted with one, or where possible, two or three substituents each independently selected from Het², R¹¹ and C_{1-4} alkyl optionally substituted with one or two substituents independently selected from Het² and R¹¹;

25 Het² represents a heterocycle selected from pyrrolyl, pyrrolinyl, imidazolyl, imidazolinyl, pyrazolyl, pyrazolinyl, triazolyl, tetrazolyl, furanyl, tetrahydrofuranyl, thienyl, thiolanyl, dioxolanyl, oxazolyl, oxazolinyl, isoxazolyl, thiazolyl, thiazolinyl, isothiazolyl, thiadiazolyl, oxadiazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyranyl, pyridazinyl, dioxanyl, dithianyl, trithianyl, triazinyl, benzothienyl, isobenzothienyl, benzofuranyl, isobenzofuranyl, benzothiazolyl, benzoxazolyl, indolyl, isoindolyl, indolinyl, purinyl, 1*H*-pyrazolo[3,4-d]pyrimidinyl, benzimidazolyl, quinolyl, isoquinolyl, cinnolinyl, phtalazinyl, quinazolinyl, quinoxalinyl, thiazolopyridinyl, oxazolopyridinyl and imidazo[2,1-b]thiazolyl; wherein said heterocycles each independently may optionally be

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substituted with one, or where possible, two or three substituents each independently selected from R^{11} and C_{1-4} alkyl optionally substituted with one or two substituents independently selected from R^{11} ;

5 Het³ represents a monocyclic heterocycle selected from pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl and tetrahydropyran; wherein said monocyclic heterocycles each independently may optionally be substituted with, where possible, one, two, three or four substituents each independently selected from hydroxy, C_{1-4} alkyl, C_{1-4} alkyloxy, C_{1-4} alkylcarbonyl, piperidinyl, $NR^{12}R^{13}$, $C(=O)-O-R^{14}$, R^6 and C_{1-4} alkyl substituted with one or two substituents independently selected from hydroxy, C_{1-4} alkyloxy, phenyl, $10 C(=O)-O-R^{14}$, $-Y-C_{1-4}$ alkanediyl- $C(=O)-O-R^{14}$, R^5 and $NR^{12}R^{13}$;

Het⁴ represents a monocyclic heterocycle selected from pyrrolyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl, furanyl, thienyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, thia-diazolyl, oxadiazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyranyl, pyridazinyl and triazinyl.

15 As used in the foregoing definitions and hereinafter, halo is generic to fluoro, chloro, bromo and iodo; C_{3-7} cycloalkyl is generic to cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl; C_{1-4} alkyl defines straight and branched chain saturated hydrocarbon radicals having from 1 to 4 carbon atoms such as, for example, methyl, ethyl, propyl, butyl, 1-methylethyl, 2-methylpropyl, 2,2-dimethylethyl and the like; C_{1-6} alkyl is meant to include C_{1-4} alkyl and the higher homologues thereof having 5 or 6 carbon atoms such as, for example, pentyl, 2-methylbutyl, hexyl, 2-methylpentyl and the like; polyhalo C_{1-4} alkyl is defined as polyhalosubstituted C_{1-4} alkyl, in particular C_{1-4} alkyl substituted with 1 to 6 halogen atoms, more in particular difluoro- or trifluoromethyl; polyhalo C_{1-6} alkyl is defined as polyhalosubstituted C_{1-6} alkyl. The term C_{1-4} alkanediyl defines bivalent straight or branch chained alkanediyl radicals having from 1 to 4 carbon atoms such as, for example, methylene, 1,2-ethanediyl, 1,3-propanediyl, 1,4-butanediyl and the like; C_{2-6} alkanediyl defines bivalent straight or branch chained alkanediyl radicals having from 2 to 6 carbon atoms such as, for example, 1,2-ethanediyl, 1,3-propanediyl, 1,4-butanediyl, 1,5-pentanediyl, 1,6-hexanediyl and the like.

20 C_{1-4} alkyl, C_{1-6} alkyl, C_{1-4} alkanediyl, C_{2-6} alkanediyl, C_{1-4} alkoxy, C_{1-4} alkyloxy, C_{1-4} alkylcarbonyl, $NR^{12}R^{13}$, $C(=O)-O-R^{14}$, R^6 and C_{1-4} alkyl substituted with one or two substituents independently selected from hydroxy, C_{1-4} alkyloxy, phenyl, $10 C(=O)-O-R^{14}$, $-Y-C_{1-4}$ alkanediyl- $C(=O)-O-R^{14}$, R^5 and $NR^{12}R^{13}$ are meant to include all the possible isomeric forms of the heterocycles mentioned in the definition of Het¹, Het², Het³ and Het⁴, for instance, pyrrolyl also includes 2H-pyrrolyl; triazolyl includes 1,2,4-triazolyl and 1,3,4-triazolyl; oxadiazolyl includes 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl and 1,3,4-oxadiazolyl; thiadiazolyl includes 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,2,5-thiadiazolyl and 1,3,4-thiadiazolyl; pyranyl includes 2H-pyranyl and 4H-pyranyl.

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The heterocycles represented by Het¹, Het², Het³ and Het⁴ may be attached to the remainder of the molecule of formula (I) through any ring carbon or heteroatom as appropriate. Thus, for example, when the heterocycle is imidazolyl, it may be a 1-imidazolyl, 2-imidazolyl, 4-imidazolyl and 5-imidazolyl; when it is thiazolyl, it may be 2-thiazolyl, 4-thiazolyl and 5-thiazolyl; when it is triazolyl, it may be 1,2,4-triazol-1-yl, 1,2,4-triazol-3-yl, 1,2,4-triazol-5-yl, 1,3,4-triazol-1-yl and 1,3,4-triazol-2-yl; when it is benzthiazolyl, it may be 2-benzthiazolyl, 4-benzthiazolyl, 5-benzthiazolyl, 6-benzthiazolyl and 7-benzthiazolyl.

5 10 The pharmaceutically acceptable addition salts as mentioned hereinabove are meant to comprise the therapeutically active non-toxic acid addition salt forms which the compounds of formula (I) are able to form. The latter can conveniently be obtained by treating the base form with such appropriate acids as inorganic acids, for example, hydrohalic acids, e.g. hydrochloric, hydrobromic and the like; sulfuric acid; nitric acid; 15 phosphoric acid and the like; or organic acids, for example, acetic, propanoic, hydroxyacetic, 2-hydroxypropanoic, 2-oxopropanoic, ethanedioic, propanedioic, butanedioic, (Z)-2-butenedioic, (E)-2-butenedioic, 2-hydroxybutanedioic, 2,3-dihydroxybutanedioic, 2-hydroxy-1,2,3-propanetricarboxylic, methanesulfonic, ethanesulfonic, benzenesulfonic, 4-methylbenzenesulfonic, cyclohexanesulfamic, 2-hydroxybenzoic, 4-amino-2-hydroxybenzoic and the like acids. Conversely the salt form can be converted by treatment with alkali into the free base form.

20 25 The compounds of formula (I) containing acidic protons may be converted into their therapeutically active non-toxic metal or amine addition salt forms by treatment with appropriate organic and inorganic bases. Appropriate base salt forms comprise, for example, the ammonium salts, the alkali and earth alkaline metal salts, e.g. the lithium, sodium, potassium, magnesium, calcium salts and the like, salts with organic bases, e.g. the benzathine, N-methyl-D-glucamine, 2-amino-2-(hydroxymethyl)-1,3-propanediol, hydrabamine salts, and salts with amino acids such as, for example, arginine, lysine and the like. Conversely the salt form can be converted by treatment with acid into the free acid form.

30 35 The term addition salt also comprises the hydrates and solvent addition forms which the compounds of formula (I) are able to form. Examples of such forms are e.g. hydrates, alcoholates and the like.

The N-oxide forms of the present compounds are meant to comprise the compounds of formula (I) wherein one or several nitrogen atoms are oxidized to the so-called N-oxide.

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For example, one or more nitrogen atoms of any of the heterocycles in the definition of Het¹; Het² and Het³ may be *N*-oxidized.

Some of the compounds of formula (I) may also exist in their tautomeric forms. Such 5 forms although not explicitly indicated in the above formula are intended to be included within the scope of the present invention. For example, a hydroxy substituted triazine moiety may also exist as the corresponding triazinone moiety; a hydroxy substituted pyrimidine moiety may also exist as the corresponding pyrimidinone moiety.

10 The term "stereochemically isomeric forms" as used hereinbefore defines all the possible stereoisomeric forms in which the compounds of formula (I) can exist. Unless otherwise mentioned or indicated, the chemical designation of compounds denotes the mixture of all possible stereochemically isomeric forms, said mixtures containing all diastereomers and enantiomers of the basic molecular structure. More in particular, stereogenic centers may 15 have the R- or S-configuration, used herein in accordance with Chemical Abstracts nomenclature. Stereochemically isomeric forms of the compounds of formula (I) are obviously intended to be embraced within the scope of this invention.

20 The compounds of formula (I) and some of the intermediates in the present invention contain one or more asymmetric carbon atoms. The pure and mixed stereochemically isomeric forms of the compounds of formula (I) are intended to be embraced within the scope of the present invention.

25 Whenever used hereinafter, the term "compounds of formula (I)" is meant to also include their *N*-oxide forms, their pharmaceutically acceptable addition salts, and their stereochemically isomeric forms.

30 An interesting group of compounds are those compounds of formula (I) wherein the 6-azauracil moiety is connected to the phenyl ring in the para or meta position relative to the carbon atom bearing the -X-R², R³ and R⁴ substituents; preferably in the para position.

Another interesting group contains those compounds of formula (I) wherein one or more of the following restrictions apply :

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- p is 0, 1 or 2;
- X is S, NR⁵, or a direct bond; more in particular NH or a direct bond;
- each R¹ independently is halo, polyhaloC₁₋₆alkyl, C₁₋₆alkyl, C₁₋₆alkyloxy or aryl, preferably, chloro or trifluoromethyl, more preferably chloro;

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- R² is Het¹ or C₁₋₆alkyl substituted with one or two substituents selected from hydroxy, cyano, amino, mono- or di(C₁₋₄alkyl)amino, C₁₋₆alkyloxy, C₁₋₆alkylsulfonyloxy, C₁₋₆alkyloxycarbonyl, C₃₋₇cycloalkyl, aryl, aryloxy, arylthio, Het¹, Het¹oxy and Het¹thio; and if X is O, S or NR⁵, then R² may also represent
- 5 aminocarbonyl, aminothiocarbonyl, C₁₋₄alkylcarbonyl, C₁₋₄alkylthiocarbonyl, arylcarbonyl, arylthiocarbonyl, Het¹carbonyl or Het¹thiocarbonyl; particularly R² is Het¹ or in the event X is NH, R² may also be aminothiocarbonyl or Het¹carbonyl;
- R³ is hydrogen, methyl, ethyl, propyl or cyclohexyl; preferably, methyl;
- R⁴ is hydrogen or methyl; preferably, methyl;
- 10 • R³ and R⁴ are taken together to form a 1,4-butanediyl;
- R⁶ is C₁₋₆alkylsulfonyl or aminosulfonyl;
- R⁷ and R⁸ are each independently hydrogen, C₁₋₄alkyl, Het³ or R⁶;
- R⁹ and R¹⁰ are each independently hydrogen, C₁₋₄alkyloxyC₁₋₄alkyl, C₁₋₄alkylcarbonyl, aminocarbonyl, Het³carbonyl, Het³ or R⁶;
- 15 • R¹¹ is cyano, nitro halo, C₁₋₄alkyloxy, formyl, NR⁷R⁸, C(=O)NR⁷R⁸, -C(=O)-O-R¹⁴, aryl, arylcarbonyl, Het³, Het⁴ and C(=O)Het³;
- R¹⁴ is hydrogen or C₁₋₄alkyl;
- aryl is phenyl optionally substituted with one, two or three substituents each independently selected from nitro, cyano, halo, hydroxy, C₁₋₄alkyl, C₃₋₇cycloalkyl, C₁₋₄alkyloxy, formyl, polyhaloC₁₋₄alkyl, NR⁹R¹⁰, C(=O)NR⁹R¹⁰, C(=O)-O-R¹⁴, -O-R⁶, phenyl, C(=O)Het³ and C₁₋₄alkyl substituted with hydroxy, C₁₋₄alkyloxy, C(=O)-O-R¹⁴, Het³ or NR⁹R¹⁰;
- 20 • Het¹ is a monocyclic heterocycle selected from pyrrolyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl, furanyl, thienyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, thiadiazolyl, oxadiazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyranyl, pyridazinyl and triazinyl, in particular imidazolyl, oxadiazolyl, thiazolyl, pyrimidinyl or pyridinyl, wherein said monocyclic heterocycles each independently may optionally be substituted with one, or where possible, two or three substituents each independently selected from Het², R¹¹ and C₁₋₄alkyl optionally substituted with Het² or R¹¹; preferably
- 25 Het¹ is imidazolyl, oxadiazolyl, thiazolyl or pyridinyl each independently and optionally substituted with one, or where possible, two or three substituents each independently selected from Het², R¹¹ and C₁₋₄alkyl optionally substituted with Het² or R¹¹;
- Het² is an aromatic heterocycle; more in particular furanyl, thienyl, pyridinyl or benzothienyl, wherein said aromatic heterocycles each independently may optionally be substituted with one, or where possible, two or three substituents each independently selected from R¹¹ and C₁₋₄alkyl;
- 30 Het³ is imidazolyl, oxadiazolyl, thiazolyl or pyridinyl each independently and optionally substituted with one, or where possible, two or three substituents each independently selected from Het², R¹¹ and C₁₋₄alkyl optionally substituted with Het² or R¹¹;
- 35 Het⁴ is imidazolyl, oxadiazolyl, thiazolyl or pyridinyl each independently and optionally substituted with one, or where possible, two or three substituents each independently selected from R¹¹ and C₁₋₄alkyl;

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- Het³ is piperidinyl, piperazinyl, morpholinyl and tetrahydropyranyl each independently and optionally substituted with, where possible, one, two, three or four substituents each independently selected from hydroxy, C₁₋₄alkyl, C₁₋₄alkylcarbonyl, piperidinyl and C₁₋₄alkyl substituted with one or two substituents independently selected from hydroxy,

5 C₁₋₄alkyloxy and phenyl;

- Het⁴ is thienyl.

Special compounds are those compounds of formula (I) wherein p is 2 and both R¹ substituents are chloro; more preferably the two chloro substituents are in the ortho 10 positions relative to the carbon atom bearing the -X-R², R³ and R⁴ substituents.

Particular compounds are those compounds of formula (I) wherein the 6-azauracil moiety is in the para position relative to the carbon atom bearing the -X-R², R³ and R⁴ substituents, and p is 2 whereby both R¹ substituents are chloro positioned ortho relative 15 to the carbon atom bearing the -X-R², R³ and R⁴ substituents.

Other particular compounds are those compounds of formula (I) wherein X is a direct bond and R² is a monocyclic heterocycle selected from pyrrolyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl, furanyl, thienyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, 20 thiadiazolyl, oxadiazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyranyl, pyridazinyl and triazinyl, in particular imidazolyl, oxadiazolyl, thiazolyl, pyrimidinyl or pyridinyl, wherein said monocyclic heterocycles each independently may optionally be substituted with one, or where possible, two or three substituents each independently selected from Het², R¹¹ and C₁₋₄alkyl optionally substituted with Het² or R¹¹; more in particular R² is optionally 25 substituted thiazolyl, pyridinyl or oxadiazolyl.

Preferred compounds are those compounds of formula (I) wherein R³ and R⁴ are both methyl and -X-R² is Het¹ wherein Het¹ suitably is optionally substituted thiazolyl, pyridinyl or oxadiazolyl.

30 More preferred compounds are those compounds of formula (I) wherein R³ and R⁴ are both methyl; -X-R² is optionally substituted 2-thiazolyl or 3-oxadiazolyl, the 6-azauracil moiety is in the para position relative to the carbon atom bearing the -X-R², R³ and R⁴ substituents, and p is 2 whereby both R¹ substituents are chloro positioned ortho relative 35 to the carbon atom bearing the -X-R², R³ and R⁴ substituents.

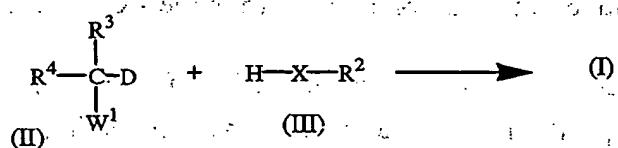
In order to simplify the structural representation of the compounds of formula (I), the group

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will hereinafter be represented by the symbol D.

Compounds of formula (I) can generally be prepared by reacting an intermediate of formula (II) wherein W^1 is a suitable leaving group such as, for example, a halogen atom, with an appropriate reagent of formula (III).



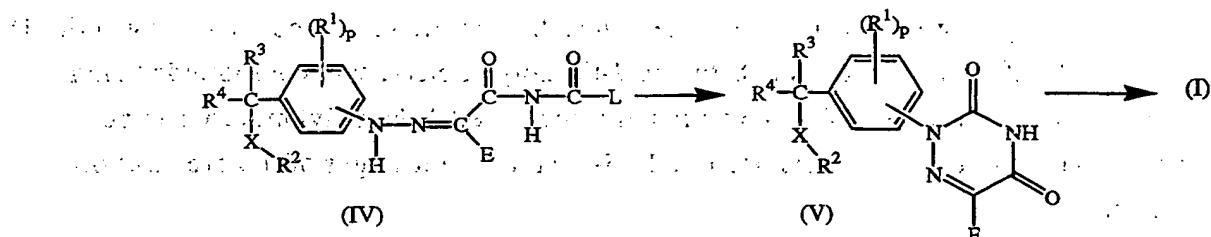
Said reaction may be performed in a reaction-inert solvent such as, for example, acetonitrile, *N,N*-dimethylformamide, acetic acid, tetrahydrofuran, ethanol or a mixture thereof. Alternatively, in case the reagent of formula (III) acts as a solvent, no additional reaction-inert solvent is required. The reaction is optionally carried out in the presence of a base such as, for example, 1,8-diazabicyclo[5.4.0]undec-7-ene, sodium bicarbonate, sodiummethanolate and the like. Convenient reaction temperatures range between -70°C and reflux temperature.

15 In this and the following preparations, the reaction products may be isolated from the reaction medium and, if necessary, further purified according to methodologies generally known in the art such as, for example, extraction, crystallization, distillation, trituration and chromatography.

20 Some of the compounds and intermediates of the present invention can be prepared according to or analogous to the procedures described in EP-A-0,170,316, EP-A-0,232,932 and PCT/EP98/04191.

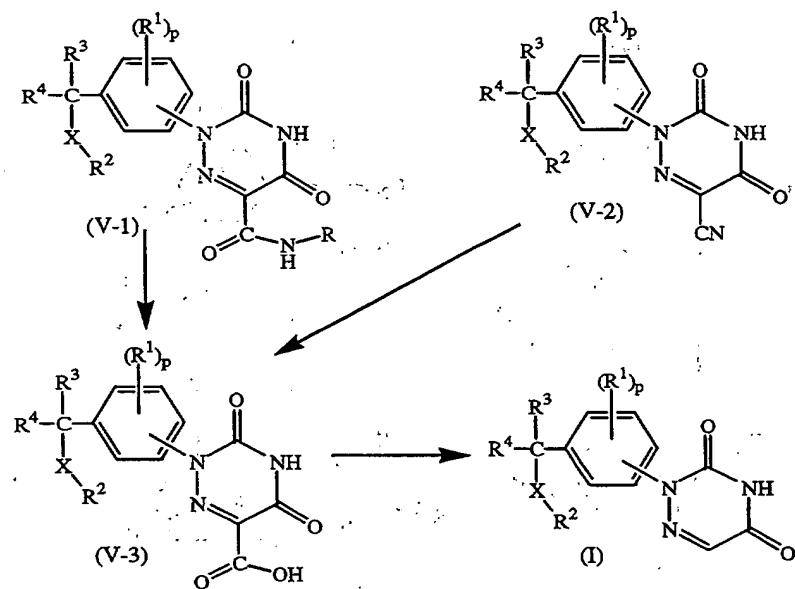
25 For instance, compounds of formula (I) may generally be prepared by cyclizing an intermediate of formula (IV) wherein L is a suitable leaving group such as, for example, C₁₋₆alkyloxy or halo, and E represents an appropriate electron attracting group such as, for example, an ester, an amide, a cyanide, C₁₋₆alkylsulfonyloxy and the like groups; and eliminating the group E of the thus obtained triazinedione of formula (V). The cyclization
 30 can suitably be carried out by refluxing the intermediate (IV) in acidic medium such as acetic acid and in the presence of a base such as, for example, potassium acetate.

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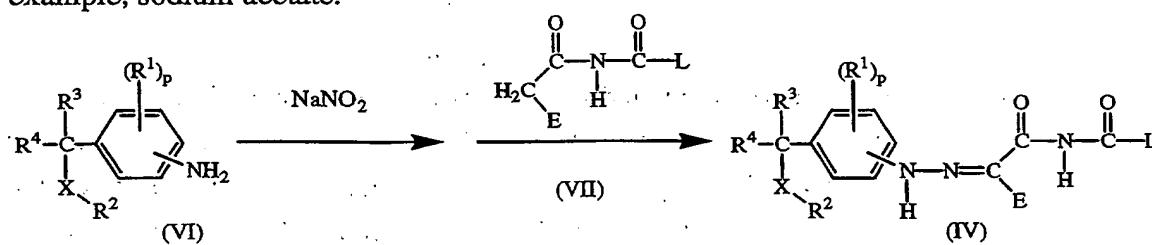
Depending on its nature, E can be eliminated using various art-known elimination procedures. For example when E is an amide or a cyano moiety, it can be hydrolyzed to a carboxylic moiety by for instance refluxing the intermediate bearing the E group in hydrochloric acid and acetic acid. The thus obtained intermediate can then be further reacted with mercaptoacetic acid or a functional derivative thereof to obtain a compound of formula (I). Said reaction is conveniently carried out at elevated temperatures ranging up to reflux temperature.

5



10 A suitable way to prepare intermediates of formula (IV) involves the reaction of an intermediate of formula (VI) with sodium nitrate or a functional derivative thereof in an acidic medium such as for example hydrochloric acid in acetic acid; and preferably in the same reaction mixture, further reacting the thus obtained intermediate with a reagent of formula (VII) wherein L and E are as defined above, in the presence of a base such as, for example, sodium acetate.

15



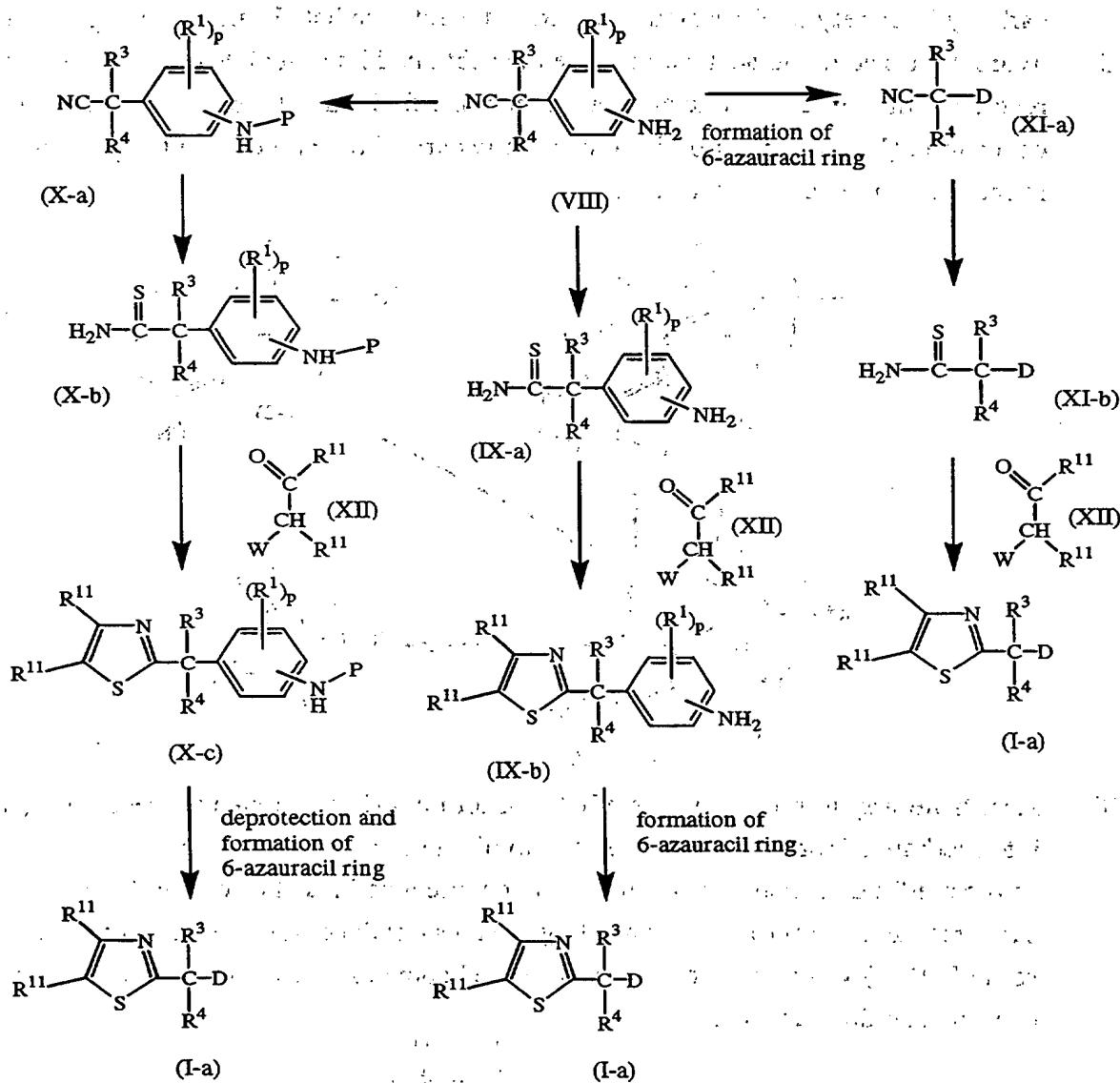
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An interesting subgroup within the present invention are those compounds of formula (I) wherein $-X-R^2$ is an optionally substituted 2-thiazolyl moiety, said compounds being represented by formula (I-a). The optionally substituted 2-thiazolyl moiety can be incorporated in the compounds of formula (I-a) at different stages of the preparation process.

5

For instance, scheme 1 depicts three possible ways to prepare compounds of formula (I-a).

Scheme 1



A first pathway involves the reaction of the cyano moiety in an intermediate of formula (VIII) to the corresponding thioamide using H_2S gas in a suitable solvent such as, for example, pyridine and in the presence of a base such as, for example, triethylamine, thus obtaining an intermediate of formula (IX-a). This thioamide can then be cyclized with

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an intermediate of formula (XII) wherein W is a suitable leaving group such as, for example, a halogen, e.g. bromo, in a suitable solvent such as, for example, ethanol. The amino moiety in the resulting 2-thiazolyl derivative of formula (IX-b) can then be further reacted as described hereinabove to form a 6-azauracil ring, thus obtaining a 5 compound of formula (I-a).

A second pathway to form compounds of formula (I-a) involves first the protecting of the amino moiety in an intermediate of formula (VIII) by introducing a suitable protective group P such as, for example, an alkylcarbonyl group, using art-known 10 protection techniques. In the example of P being a alkylcarbonyl group, the intermediates of formula (VII) can be reacted with the corresponding anhydride of formula alkyl-C(=O)-O-C(=O)-alkyl in an appropriate solvent such as, for example, toluene. The thus obtained intermediate of formula (X-a) can then be further reacted according to the first pathway described hereinabove. The final step, before formation 15 of the 6-azauracil ring can be initiated after having deprotected the amino moiety using art-known deprotection techniques. In the example of P being a alkylcarbonyl group, the intermediates of formula (X-c) may be deprotected by reacting them in a suitable solvent such as, for example, ethanol, in the presence of an acid such as, for example, hydrochloric acid.

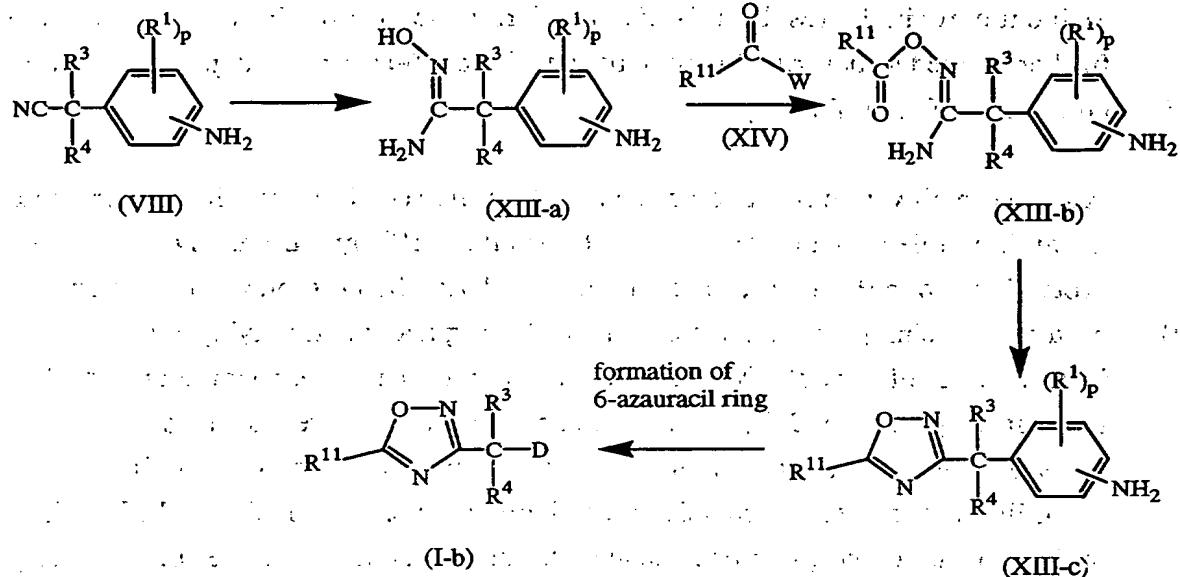
20 A third pathway involves first the formation of the 6-azauracil ring as described hereinabove but starting from an intermediate of formula (VIII), and subsequently reacting the thus formed intermediate of formula (XI-a) with H₂S and further reacting the thioamide of formula (XI-b) with an intermediate of formula (XII) as described in 25 the first pathway, to finally form a compound of formula (I-a).

Another interesting subgroup within the present invention are those compounds of 20 formula (I) wherein -X-R² is an optionally substituted 1,2,4-oxadiazol-3-yl moiety, said compounds being represented by formula (I-b-1). The optionally substituted 1,2,4-oxadiazol-3-yl moiety can be incorporated at the same stages of the reaction procedure 30 as depicted for the 2-thiazolyl derivatives in scheme 1.

For instance, analogous to one of the three pathways shown in scheme 1, compounds of 35 formula (I-b) can be performed by reacting an intermediate of formula (VIII) as depicted in scheme 2.

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Scheme 2



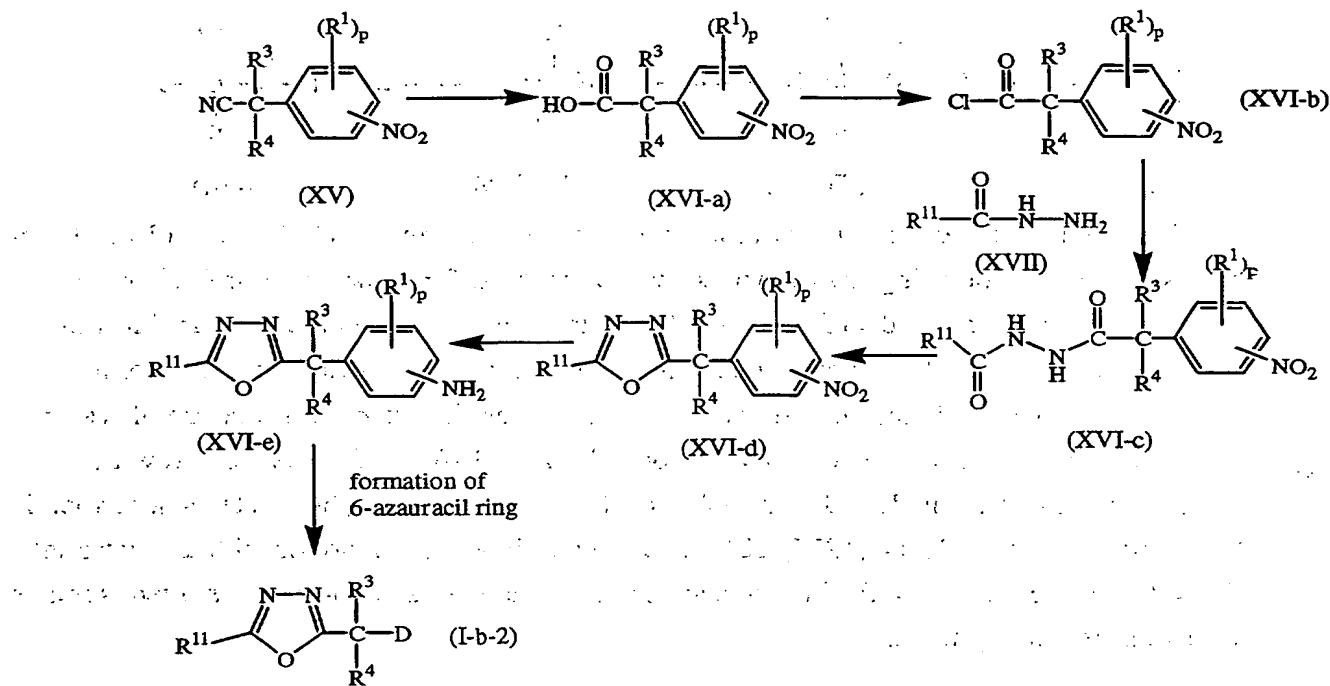
In said scheme 2, the cyano group of an intermediate of formula (VIII) is reacted with hydroxylamine or a functional derivative thereof in a suitable solvent such as, for example, methanol, and in the presence of a base such as, for example sodium methanolate. The thus formed intermediate of formula (XIII-a) is then reacted with an intermediate of formula (XIV) wherein W is a suitable leaving group such as, for example, a halogen, e.g. chloro, in an appropriate solvent such as, for example, dichloromethane, and in the presence of a base, such as, for example, *N,N*-(1-methyl-ethyl)ethaneamine. The resulting intermediate of formula (XIII-b) is then cyclized to a 3-oxadiazolyl derivative of formula (XIII-c). The amino moiety in the intermediates of formula (XIII-c) can then be transformed to the 6-azauracil ring as described above.

Still another interesting subgroup within the present invention are those compounds of formula (I) wherein $-X-R^2$ is an optionally substituted 1,3,4-oxadiazol-2-yl moiety, said compounds being represented by formula (I-b-2).

For instance, compounds of formula (I-b-2) can be prepared as depicted in scheme 3.

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Scheme 3



The nitrile moiety in an intermediate of formula (XV) is transformed into a carboxylic acid moiety using art-known techniques. For instance, the nitrile derivative may be refluxed in a mixture of sulfuric acid and acetic acid in water. The carboxylic acid

5 derivative of formula (XVI-a) may further be reacted with a chlorinating agent such as, for example, thionyl chloride, to form an acylchloride derivative of formula (XVI-b). Subsequently, The acyl chloride may be reacted with a hydrazine derivative of formula (XVII) in a suitable solvent such as, for example, dichloromethane, and in the presence of a base such as, for example N,N -(1-methylethyl)ethaneamine. The thus formed

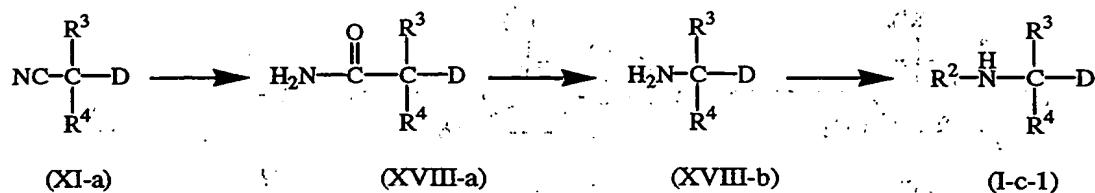
10 intermediate of formula (XVI-c) may be cyclized to a 1,2,4-oxadiazol-2-yl derivative of formula (XVI-d) in the presence of phosphoryl chloride. As a final step before the formation of the 6-azauracil ring as described above, the nitro group in the intermediates of formula (XVI-e) is reduced to an amino group using art-known reduction techniques such as, for instance, reducing the nitro group with hydrogen in methanol and in the

15 presence of a catalyst such as Raney Nickel.

Yet another interesting subgroup within the present invention are those compounds of formula (I) wherein $-\text{X}-\text{R}^2$ is $-\text{NH}-\text{R}^2$, said compounds being represented by formula (I-c-1). Scheme 4 depicts a suitable pathway to obtain compounds of formula (I-c-1).

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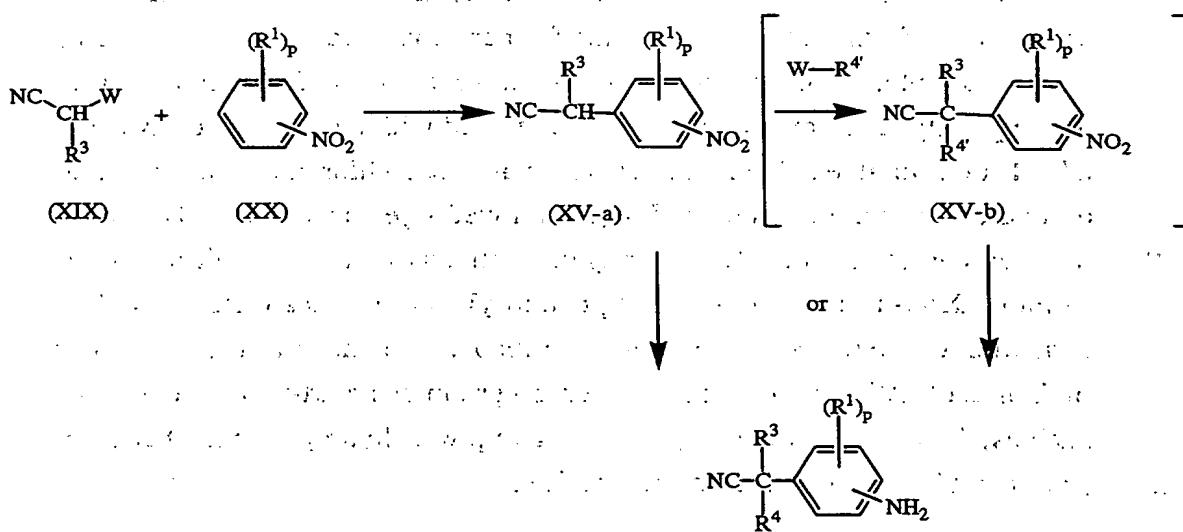
Scheme 4



In said scheme 4, the cyano moiety of an intermediate of formula (XI-a) is hydrolyzed to the corresponding amide using art-known techniques such as, for instance, hydrolysis in the presence of acetic acid and sulfuric acid. The thus formed amide in the intermediates of formula (XVIII-a) can be transformed in an amine using (diacetoxyiodo)benzene or a functional derivative thereof in a suitable solvent such as, for example a mixture of water and acetonitrile. The amine derivative of formula (XVIII-b) can then be reacted with benzotriazol-1-yloxytris(dimethylamino) phosphonium hexafluorophosphate as described in Tetrahedron Letters No.14 (1975) 1219-1222 to obtain a compound, or with a functional derivative thereof such as, for instance, an isothiocyanate, in an appropriate solvent such as, for example, tetrahydrofuran.

Intermediates of formula (VIII) can be prepared as depicted in scheme 5.

Scheme 5



15

(VIII)

An intermediate of formula (XIX) and an intermediate of formula (XX) may be reacted in a suitable solvent such as, for example, dimethylsulfoxide, in the presence of a base such as, for example sodium hydroxide, to form an intermediate of formula (XV-a). The nitro moiety in the intermediates of formula (XV-a) may either be immediately reduced

to an amino group using art-known reduction techniques such as, for example, reducing the nitro group with hydrogen in methanol and in the presence of a catalyst such as Raney Nickel, or may first be reacted with an intermediate of formula $R^{4'}-W$ wherein $R^{4'}$ is the same as R^4 but other than hydrogen and W is a suitable leaving group such as, for example, a halogen, e.g. iodo, in a suitable solvent such as, for example, N,N -dimethylformamide, and in the presence of a suitable base such as, for example, sodium hydride, before reducing the nitro moiety.

The compounds of formula (I) can also be converted into each other following art-known procedures of functional group transformation such as, for example, those mentioned in PCT/EP98/04191 and the ones exemplified in the experimental part hereinafter.

The compounds of formula (I) may also be converted to the corresponding *N*-oxide forms following art-known procedures for converting a trivalent nitrogen into its *N*-oxide form. Said *N*-oxidation reaction may generally be carried out by reacting the starting material of formula (I) with 3-phenyl-2-(phenylsulfonyl)oxaziridine or with an appropriate organic or inorganic peroxide. Appropriate inorganic peroxides comprise, for example, hydrogen peroxide, alkali metal or earth alkaline metal peroxides; e.g. sodium peroxide, potassium peroxide; appropriate organic peroxides may comprise peroxy acids such as, for example, benzenecarboperoxoic acid or halo substituted benzenecarboperoxoic acid, e.g. 3-chlorobenzenecarboperoxoic acid, peroxyalkanoic acids, e.g. peroxyacetic acid, alkylhydroperoxides, e.g. *t*-butyl hydroperoxide. Suitable solvents are, for example, water, lower alkanols; e.g. ethanol and the like, hydrocarbons, e.g. toluene, ketones, e.g. 2-butanone, halogenated hydrocarbons, e.g. dichloromethane, and mixtures of such solvents.

Pure stereochemically isomeric forms of the compounds of formula (I) may be obtained by the application of art-known procedures. Diastereomers may be separated by physical methods such as selective crystallization and chromatographic techniques, e.g. counter-current distribution, liquid chromatography and the like.

Some of the compounds of formula (I) and some of the intermediates in the present invention may contain an asymmetric carbon atom. Pure stereochemically isomeric forms of said compounds and said intermediates can be obtained by the application of art-known procedures. For example, diastereoisomers can be separated by physical methods such as selective crystallization or chromatographic techniques, e.g. counter current distribution, liquid chromatography and the like methods. Enantiomers can be obtained from racemic mixtures by first converting said racemic mixtures with suitable resolving agents such as, for example, chiral acids, to mixtures of diastereomeric salts or compounds; then

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physically separating said mixtures of diastereomeric salts or compounds by, for example, selective crystallization or chromatographic techniques, e.g. liquid chromatography and the like methods; and finally converting said separated diastereomeric salts or compounds into the corresponding enantiomers. Pure stereochemically isomeric forms may also be
5 obtained from the pure stereochemically isomeric forms of the appropriate intermediates and starting materials, provided that the intervening reactions occur stereospecifically.

An alternative manner of separating the enantiomeric forms of the compounds of formula (I) and intermediates involves liquid chromatography, in particular liquid chromatography
10 using a chiral stationary phase.

Some of the intermediates and starting materials as used in the reaction procedures mentioned hereinabove are known compounds and may be commercially available or may be prepared according to art-known procedures.

15 IL-5, also known as eosinophil differentiating factor (EDF) or eosinophil colony stimulating factor (Eo-CSF), is a major survival and differentiation factor for eosinophils and therefore thought to be a key player in eosinophil infiltration into tissues. There is ample evidence that eosinophil influx is an important pathogenic event in bronchial
20 asthma and allergic diseases such as, cheilitis, irritable bowel disease, eczema, urticaria, vasculitis, vulvitis, winterfeet, atopic dermatitis, pollinosis, allergic rhinitis and allergic conjunctivitis; and other inflammatory diseases, such as eosinophilic syndrome, allergic angiitis; eosinophilic fasciitis; eosinophilic pneumonia, PIE syndrome, idiopathic eosinophilia, eosinophilic myalgia, Crohn's disease, ulcerative colitis and the like diseases.
25

30 The present compounds also inhibit the production of other chemokines such as monocyte chemotactic protein-1 and -3 (MCP-1 and MCP-3). MCP-1 is known to attract both T-cells, in which IL-5 production mainly occurs, and monocytes, which are known to act synergistically with eosinophils (Carr et al., 1994, Immunology, 91, 3652-3656). MCP-3 also plays a primary role in allergic inflammation as it is known to mobilize and activate basophil and eosinophil leukocytes (Baggiolini et al., 1994, Immunology Today, 15(3), 127-133).

35 The present compounds have no or little effect on the production of other chemokines such as IL-1, IL-2, IL-3, IL-4, IL-6, IL-10, γ -interferon (IFN- γ) and granulocyte-macrophage colony stimulating factor (GM-CSF) indicating that the present IL-5 inhibitors do not act as broad-spectrum immunosuppressives.

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1 The selective chemokine inhibitory effect of the present compounds can be demonstrated
2 by *in vitro* chemokine measurements in human blood of which the test results for IL-5 are
3 presented in the experimental part hereinafter. *In vivo* observations such as the inhibition
4 of eosinophilia in mouse ear, the inhibition of blood eosinophilia in the *Ascaris* mouse
5 model; the reduction of serum IL-5 protein production and splenic IL-5 mRNA
6 expression induced by anti-CD3 antibody in mice and the inhibition of allergen- or
7 Sephadex-induced pulmonary influx of eosinophils in guinea-pig are indicative for the
8 usefulness of the present compounds in the treatment of eosinophil-dependent
9 inflammatory diseases.

10 The present inhibitors of IL-5 production are orally active compounds.

11 The intermediates of formula (XI-a) are interesting intermediates. Not only have they a
12 particular usefulness as intermediates in the preparation of the compounds of formula (I),
13 they also have valuable pharmacological activity.

14 In view of the above pharmacological properties, the compounds of formula (I) can be
15 used as a medicine. In particular, the present compounds can be used in the manufacture
16 of a medicament for treating eosinophil-dependent inflammatory diseases as mentioned
17 hereinabove, more in particular bronchial asthma, atopic dermatitis, allergic rhinitis and
18 allergic conjunctivitis.

19 In view of the utility of the compounds of formula (I), there is provided a method of
20 treating warm-blooded animals, including humans, suffering from eosinophil-dependent
21 inflammatory diseases, in particular bronchial asthma, atopic dermatitis, allergic rhinitis
22 and allergic conjunctivitis. Said method comprises the systemic or topical administration
23 of an effective amount of a compound of formula (I), a *N*-oxide form, a pharmaceutically
24 acceptable addition salt or a possible stereoisomeric form thereof, to warm-blooded
25 animals, including humans.

26 The present invention also provides compositions for treating eosinophil-dependent
27 inflammatory diseases comprising a therapeutically effective amount of a compound of
28 formula (I) and a pharmaceutically acceptable carrier or diluent.

29 To prepare the pharmaceutical compositions of this invention, a therapeutically effective
30 amount of the particular compound, in base form or addition salt form, as the active
31 ingredient is combined in intimate admixture with a pharmaceutically acceptable carrier,
32 which may take a wide variety of forms depending on the form of preparation desired for
33 administration. These pharmaceutical compositions are desirably in unitary dosage form

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suitable, preferably, for systemic administration such as oral, percutaneous, or parenteral administration; or topical administration such as via inhalation, a nose spray, eye drops or via a cream, gel, shampoo or the like. For example, in preparing the compositions in oral dosage form, any of the usual pharmaceutical media may be employed, such as, for 5 example, water, glycols, oils, alcohols and the like in the case of oral liquid preparations such as suspensions, syrups, elixirs and solutions: or solid carriers such as starches, sugars, kaolin, lubricants, binders, disintegrating agents and the like in the case of powders, pills, capsules and tablets. Because of their ease in administration, tablets and capsules represent the most advantageous oral dosage unit form, in which case solid 10 pharmaceutical carriers are obviously employed. For parenteral compositions, the carrier will usually comprise sterile water, at least in large part, though other ingredients, for example, to aid solubility, may be included. Injectable solutions, for example, may be prepared in which the carrier comprises saline solution, glucose solution or a mixture of saline and glucose solution. Injectable suspensions may also be prepared in which case 15 appropriate liquid carriers, suspending agents and the like may be employed. In the compositions suitable for percutaneous administration, the carrier optionally comprises a penetration enhancing agent and/or a suitable wettable agent, optionally combined with suitable additives of any nature in minor proportions, which additives do not cause any significant deleterious effects on the skin. Said additives may facilitate the administration 20 to the skin and/or may be helpful for preparing the desired compositions. These compositions may be administered in various ways, e.g., as a transdermal patch, as a spot-on or as an ointment. As appropriate compositions for topical application there may be cited all compositions usually employed for topically administering drugs e.g. creams, gellies, dressings, shampoos, tinctures, pastes, ointments, salves, powders and the like. 25 Application of said compositions may be by aerosol, e.g. with a propellant such as nitrogen, carbon dioxide, a freon; or without a propellant such as a pump spray, drops, lotions, or a semisolid such as a thickened composition which can be applied by a swab. In particular, semisolid compositions such as salves, creams, gellies, ointments and the like will conveniently be used.

30 It is especially advantageous to formulate the aforementioned pharmaceutical compositions in dosage-unit form for ease of administration and uniformity of dosage. Dosage unit form as used in the specification and claims herein refers to physically discrete units suitable as unitary dosages, each unit containing a predetermined quantity of active ingredient calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. Examples of such dosage unit forms are tablets (including scored or coated tablets), capsules, pills, powder packets, wafers, injectable

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solutions or suspensions, teaspoonfuls, tablespoonfuls and the like, and segregated multiples thereof.

In order to enhance the solubility and/or the stability of the compounds of formula (I) in pharmaceutical compositions, it can be advantageous to employ α -, β - or γ -cyclodextrins or their derivatives. Also co-solvents such as alcohols may improve the solubility and/or the stability of the compounds of formula (I) in pharmaceutical compositions. In the preparation of aqueous compositions, addition salts of the subject compounds are obviously more suitable due to their increased water solubility.

Appropriate cyclodextrins are α -, β -, γ -cyclodextrins or ethers and mixed ethers thereof wherein one or more of the hydroxy groups of the anhydroglucose units of the cyclodextrin are substituted with C₁₋₆alkyl, particularly methyl, ethyl or isopropyl, e.g. randomly methylated β -CD; hydroxyC₁₋₆alkyl, particularly hydroxyethyl, hydroxypropyl or hydroxybutyl; carboxyC₁₋₆alkyl, particularly carboxymethyl or carboxy-ethyl; C₁₋₆alkylcarbonyl, particularly acetyl; C₁₋₆alkyloxycarbonylC₁₋₆alkyl or carboxy-C₁₋₆alkyloxyC₁₋₆alkyl, particularly carboxymethoxypropyl or carboxyethoxypropyl; C₁₋₆alkylcarbonyloxyC₁₋₆alkyl, particularly 2-acetyloxypropyl. Especially noteworthy as complexants and/or solubilizers are β -CD, randomly methylated β -CD, 2,6-dimethyl- β -CD, 2-hydroxyethyl- β -CD, 2-hydroxyethyl- γ -CD, 2-hydroxypropyl- γ -CD and (2-carboxymethoxy)propyl- β -CD, and in particular 2-hydroxypropyl- β -CD (2-HP- β -CD).

The term mixed ether denotes cyclodextrin derivatives wherein at least two cyclodextrin hydroxy groups are etherified with different groups such as, for example, hydroxypropyl and hydroxyethyl.

The average molar substitution (M.S.) is used as a measure of the average number of moles of alkoxy units per mole of anhydroglucose. The M.S. value can be determined by various analytical techniques, preferably, as measured by mass spectrometry, the M.S. ranges from 0.125 to 10.

The average substitution degree (D.S.) refers to the average number of substituted hydroxyls per anhydroglucose unit. The D.S. value can be determined by various analytical techniques, preferably, as measured by mass spectrometry, the D.S. ranges from 0.125 to 3.

Due to their high degree of selectivity as IL-5 inhibitors, the compounds of formula (I) as defined above, are also useful to mark or identify receptors. To this purpose, the

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compounds of the present invention need to be labelled, in particular by replacing, partially or completely, one or more atoms in the molecule by their radioactive isotopes. Examples of interesting labelled compounds are those compounds having at least one halo which is a radioactive isotope of iodine, bromine or fluorine; or those compounds 5 having at least one ^{11}C -atom or tritium atom.

One particular group consists of those compounds of formula (I) wherein R^3 and/or R^4 are a radioactive halogen atom. In principle, any compound of formula (I) containing a halogen atom is prone for radiolabelling by replacing the halogen atom by a suitable 10 isotope. Suitable halogen radioisotopes to this purpose are radioactive iodides, e.g. ^{122}I , ^{123}I , ^{125}I , ^{131}I ; radioactive bromides, e.g. ^{75}Br , ^{76}Br , ^{77}Br and ^{82}Br ; and radioactive fluorides, e.g. ^{18}F . The introduction of a radioactive halogen atom can be performed by a suitable exchange reaction or by using any one of the procedures as described hereinabove to prepare halogen derivatives of formula (I).

15 Another interesting form of radiolabelling is by substituting a carbon atom by a ^{11}C -atom or the substitution of a hydrogen atom by a tritium atom.

Hence, said radiolabelled compounds of formula (I) can be used in a process of 20 specifically marking receptor sites in biological material. Said process comprises the steps of (a) radiolabelling a compound of formula (I), (b) administering this radiolabelled compound to biological material and subsequently (c) detecting the emissions from the radiolabelled compound. The term biological material is meant to comprise every kind of material which has a biological origin. More in particular this term refers 25 to tissue samples, plasma or body fluids but also to animals, specially warm-blooded animals, or parts of animals such as organs.

The radiolabelled compounds of formula (I) are also useful as agents for screening 30 whether a test compound has the ability to occupy or bind to a particular receptor site. The degree to which a test compound will displace a compound of formula (I) from such a particular receptor site will show the test compound ability as either an agonist, an antagonist or a mixed agonist/antagonist of said receptor.

When used in *in vivo* assays, the radiolabelled compounds are administered in an appropriate composition to an animal and the location of said radiolabelled compounds is detected using imaging techniques, such as, for instance, Single Photon Emission 35 Computerized Tomography (SPECT) or Positron Emission Tomography (PET) and the like. In this manner the distribution of the particular receptor sites throughout the body can be detected and organs containing said receptor sites can be visualized by the imaging techniques mentioned hereinabove. This process of imaging an organ by

administering a radiolabelled compound of formula (I) and detecting the emissions from the radioactive compound also constitutes a part of the present invention.

In general, it is contemplated that a therapeutically effective daily amount would be from 5 0.01 mg/kg to 50 mg/kg body weight, in particular from 0.05 mg/kg to 10 mg/kg body weight. A method of treatment may also include administering the active ingredient on a regimen of between two or four intakes per day.

Experimental part

10 In the examples hereinafter, "DMSO" stands for dimethylsulfoxide, "RT" stands for room temperature, "DMF" stand for *N,N*-dimethylformamide, "EtOAc" stands for ethylacetate, "DIPE" stands for diisopropylether and "THF" stands for tetrahydrofuran.

A. Preparation of the intermediate compounds

Example A1

15 a) A mixture of 2-chloropropanenitrile (0.2 mol) and 1,3-dichloro-5-nitrobenzene (0.2 mol) in DMSO (50ml) was added dropwise at RT to a solution of NaOH (1 mol) in DMSO (150ml) while the temperature was kept below 30°C. The mixture was stirred at RT for 1 hour, then poured out on ice and acidified with HCl. The precipitate was filtered off, washed with H₂O and taken up in CH₂Cl₂. The organic solution was washed 20 with H₂O, dried, filtered and the solvent was evaporated. The residue was purified by column chromatography over silica gel (eluent: CH₂Cl₂/cyclohexane 70/30). The pure fractions were collected and the solvent was evaporated, yielding 19.5 g (40%) of (±)-2,6-dichloro- α -methyl-4-nitrobenzenecetonitrile (interm. 1).

25 b) NaH 80% (0.0918 mol) was added portionwise at 0°C under N₂ flow to a solution of intermediate (1) (0.0612 mol) in DMF (100ml). The mixture was stirred at 0°C under N₂ flow for 1 hour. CH₃I (0.0918 mol) was added dropwise at 0°C. The mixture was stirred at 50°C for 12 hours, then poured out on ice and extracted with EtOAc. The organic layer was separated, washed with H₂O, dried, filtered and the solvent was evaporated, yielding 17.1g of 2,6-dichloro- α,α -dimethyl-4-nitrobenzenecetonitrile (interm. 2).

30 c) A mixture of intermediate (2) (0.066 mol) in CH₃OH (200ml) was hydrogenated at RT under a 3 bar pressure for 1 hour with Raney Nickel (15g) as a catalyst. After uptake of H₂, the catalyst was filtered through celite, washed with CH₃OH and the filtrate was evaporated, yielding 17.1g of 4-amino-2,6-dichloro- α,α -dimethylbenzenecetonitrile (interm. 3).

35 d) Acetic acid anhydride (0.1484 mol) was added dropwise at RT to a solution of 4-amino-2,6-dichloro- α,α -dimethylbenzenecetonitrile (0.0742 mol) in toluene (200ml). The mixture was stirred and refluxed for 4 hours. The solvent was evaporated and the

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residue was taken up in CH_2Cl_2 . The organic solution was washed with K_2CO_3 10% and with H_2O , dried, filtered and the solvent was evaporated, yielding 19.0 g (95%) of *N*-[3,5-dichloro-4-(1-cyano-1-methylethyl)phenyl]acetonitrile (interm. 4).

e) A mixture of intermediate (4) (0.07 mol) and triethylamine (0.07 mol) in pyridine (150ml) was stirred at 60°C. H_2S was bubbled through the mixture. The mixture was stirred at 60°C for 24 hours. H_2S was bubbled through the mixture for another 24 hours. The solvent was evaporated and the residue was taken up in CH_2Cl_2 and CH_3OH . The organic solution was washed with HCl 3N and with H_2O , dried, filtered and the solvent was evaporated. The residue was crystallized from diethyl ether. The precipitate was filtered off and dried, yielding 14.7g (69%) of *N*-[4-[1-(aminosulfinyl)-1-methylethyl]-3,5-dichlorophenyl]acetamide (interm. 5).

f) A mixture of intermediate (5) (0.0481 mol) and 2-bromo-1-phenylethanone (0.0529 mol) in ethanol (300ml) was stirred and refluxed for 4 hours. The solvent was evaporated. The residue was taken up in CH_2Cl_2 . The organic solution was washed with H_2O , dried, filtered and the solvent was evaporated, yielding 20.0g of *N*-[3,5-dichloro-4-[1-methyl-1-(4-phenyl-2-thiazolyl)ethyl]phenyl]acetamide (interm. 6).

g) A mixture of intermediate (6) (0.0493 mol) in HCl-3N (200ml) and ethanol (300ml) was stirred at 60°C for 12 hours. The solvent was evaporated. The residue was basified with a concentrated NH_4OH solution and extracted with CH_2Cl_2 . The organic layer was separated, washed with H_2O , dried, filtered and the solvent was evaporated. The residue was purified by column chromatography over silica gel (eluent: CH_2Cl_2 /cyclohexane, 70/30). The pure fractions were collected and the solvent was evaporated, yielding 6.5 g (36%) of 3,5-dichloro-4-[1-methyl-1-(4-phenyl-2-thiazolyl)ethyl]benzeneamine (interm. 7).

h) A solution of NaNO_2 (0.017 mol) in a small amount of H_2O was added at 5°C to a solution of intermediate (7) (0.017 mol) in acetic acid (50ml) and concentrated HCl (10ml). The mixture was stirred at 0°C for 35 minutes and then added to a solution of ethyl cyanoacetylcarbamate (0.0238 mol) and sodium acetate (62g) in water (700ml). The mixture was stirred at 0°C for 45 minutes. The precipitate was filtered off, washed with H_2O and centrifuged. The residue was taken up in EtOAc . The organic solution was washed with H_2O , dried, filtered and the solvent was evaporated, yielding 7.6 g (84%) of ethyl [[[3,5-dichloro-4-[1-methyl-1-(4-phenyl-2-thiazolyl)ethyl]phenyl]-hydrazono]cyanoacetyl]carbamate (interm. 8).

i) A mixture of intermediate (8) (0.0143 mol) and potassium acetate (0.015 mol) in acetic acid (70ml) was stirred and refluxed for 3 hours and poured out into H_2O . The precipitate was filtered off and taken up in EtOAc . The organic solution was washed with H_2O , dried, filtered and the solvent was evaporated, yielding 8.3 g of 2-[3,5-dichloro-4-

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[1-methyl-1-(4-phenyl-2-thiazolyl)ethyl]phenyl]-2,3,4,5-tetrahydro-3,5-dioxo-1,2,4-triazine-6-carbonitrile (interm. 9).

j) A mixture of intermediate (9) (0.0171 mol) in concentrated HCl (25ml) and acetic acid (75ml) was stirred and refluxed for 3 hours. The mixture was cooled and poured out into H₂O. The precipitate was filtered off, washed with H₂O and taken up in EtOAc. The organic solution was dried, filtered and the solvent was evaporated, yielding 6.8 g (79%) of 2-[3,5-dichloro-4-[1-methyl-1-(4-phenyl-2-thiazolyl)ethyl]phenyl]-2,3,4,5-tetrahydro-3,5-dioxo-1,2,4-triazine-6-carboxylic acid (interm. 10).

Example A2

a) A solution of NaNO₂ (0.36 mol) in H₂O (50 ml) was added to a solution of intermediate (3) (0.34 mol) in acetic acid (700 ml) and HCl (102 ml); stirred at 10°C. The reaction mixture was stirred for 80 minutes at 10°C. A powdered mixture of sodium acetate (1.02 mol) and diethyl(1,3-dioxo-1,3-propanediyl)bis carbamate (0.374 mol) was added and the reaction mixture was stirred for 40 minutes. The reaction mixture was poured out onto crushed ice. The precipitate was filtered off, washed with water, taken up into CH₂Cl₂, and the layers were separated. The organic layer was dried, filtered and the solvent evaporated, yielding 138.5 g (84%) of diethyl *N,N*-[2-[3,5-dichloro-4-(1-cyano-1-methylethyl)phenyl]hydrazone]-1,3-dioxo-1,3-propanediyl]dicarbamate (interm. 11).

b) A solution of intermediate (11) (0.28 mol) and potassium acetate (0.28 mol) in acetic acid (1000 ml) was stirred and refluxed for 3 hours. The reaction mixture containing ethyl [[2-[3,5-dichloro-4-(1-cyano-1-methylethyl)phenyl]-2,3,4,5-tetrahydro-3,5-dioxo-1,2,4-triazin-6-yl]carbonyl]carbamate (interm. 12) was used as such in the next step.

c) Intermediate (12) (crude reaction mixture) was treated with HCl 36% (0.84 mol). The reaction mixture was stirred and refluxed for 4 hours, then stirred at RT over the weekend. The reaction mixture was poured out onto crushed ice and this mixture was extracted with CH₂Cl₂. The separated organic layer was dried, filtered and the solvent evaporated, yielding 111.6 g of 2-[3,5-dichloro-4-(1-cyano-1-methylethyl)phenyl]-2,3,4,5-tetrahydro-3,5-dioxo-1,2,4-triazine-6-carboxylic acid (interm. 13).

d) A suspension of intermediate (13) (0.28 mol) in mercaptoacetic acid (250.0 ml) was stirred for 4 hours at 100 °C, then allowed to cool to RT and stirred overnight. The reaction mixture was poured out onto crushed ice and this mixture was extracted with CH₂Cl₂. The separated organic layer was dried, filtered and the solvent evaporated. Toluene was added and azeotroped on the rotary evaporator. The residue was purified by short column chromatography over silica gel (eluent: CH₂Cl₂/CH₃OH 98/2). The pure fractions were collected and the solvent was evaporated. The residue was stirred in DIPE, filtered off, washed with DIPE, then dried, yielding 36.8 g (41%) of 2,6-dichloro-

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4-(4,5-dihydro-3,5-dioxo-1,2,4-triazin-2(3H)-yl)- α , α -dimethylbenzeneacetonitrile. The filtrate was stirred in DIPE and the resulting precipitate was filtered off, washed with DIPE, and dried, yielding 2.5 g (3%) of 2,6-dichloro-4-(4,5-dihydro-3,5-dioxo-1,2,4-triazin-2(3H)-yl)- α , α -dimethylbenzeneacetonitrile (interm. 14).

5 e) A solution of intermediate (14) (0.107 mol) and *N,N*-bis(1-methylethyl)ethanamine (0.315 mol) in pyridine (500 ml) was stirred and heated to 80°C. H₂S was allowed to bubble through this solution for 24 hours at 80°C. H₂S gas inlet was stopped and the reaction mixture was stirred over the weekend at RT. The solvent was evaporated. CH₂Cl₂/CH₃OH (500 ml; 9:1) was added, and this mixture was poured out into 2 N HCl (1000 ml) at 0°C. The mixture was stirred for 10 minutes. The precipitate was filtered off and dried, yielding 23.2 g (64%) of 2,6-dichloro-4-(4,5-dihydro-3,5-dioxo-1,2,4]- α , α -dimethylbenzeneethanethioamide (interm. 15).

Example A3

a) A solution of intermediate (3) (0.1484 mol) and triethylamine (0.15 mol) in pyridine (300 ml) was stirred at 60°C. H₂S was allowed to bubble through the mixture for 4 days. More triethylamine (20 ml) was added and the reaction mixture was stirred for 24 hours. More triethylamine (10 ml) was added and H₂S was bubbled through the mixture at 60°C. The solvent was evaporated. The residue was taken up into CH₂Cl₂ with a small amount of CH₃OH. The organic solution was washed with 3 N HCl and precipitation resulted.

20 The precipitate was filtered off and was taken up into CH₂Cl₂/CH₃OH (9:1), washed with NaHCO₃, with water, dried, filtered and the solvent was evaporated. The residue was boiled in diethyl ether, filtered off and dried, yielding 14.1 g (37%) of 4-amino-2,6-dichloro- α , α -dimethylbenzeneethanethioamide (interm. 16).

b) A mixture of intermediate (16) (0.04271 mol) and 3-amino-2-bromo-1-phenylpropanone (0.043 mol) in ethanol (150 ml) was stirred for 4 hours at 50°C under N₂ atmosphere. The solvent was evaporated and a 10% aqueous K₂CO₃ solution was added and this mixture was extracted with CH₂Cl₂. The separated organic layer was dried, filtered and the solvent evaporated. The residue was purified by column chromatography over silica gel (eluent: CH₂Cl₂/CH₃OH from 100/0 to 97/3). The pure fractions were

25 collected and the solvent was evaporated. The residue was dissolved in 2-propanol and converted into the hydrochloric acid salt (1:1) with 6 N HCl/ 2-propanol). The solvent was evaporated. The residue was recrystallized from 2-propanol. The precipitate was filtered off and dried, yielding 6.7 g (35%) of 2-[1-(4-amino-2,6-dichlorophenyl)-1-methylethyl-*N,N*-dimethyl-4-phenyl-5-hiazolemethanamine (interm. 17).

30 c) At 10 °C, intermediate (17) (0.0141 mol) was stirred in a mixture of acetic acid (50 ml) and HCl, 37% (4.23 ml). A solution of NaNO₂ (0.01414 mol) in water (5 ml) was added dropwise over 15 minutes at 10°C. The reaction mixture was stirred for 1

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hour at 10°C. Sodium acetate (0.0475 mol) and diethyl(1,3-dioxo-1,3-propanediyl)-biscarbamate (0.016 mol) were added in one portion and the resulting reaction mixture was stirred for one hour at RT. The reaction mixture was poured into ice-water (400 ml). CH_2Cl_2 (400 ml) was added and the aqueous layer was alkalized with solid NaHCO_3 . The separated organic layer was dried, filtered and the solvent evaporated, yielding 10.0 g of diethyl N,N -[2-[[3,5-dichloro-4-[1-[5-[(dimethylamino)methyl-4-phenyl-2-thiazolyl]-1-methylethyl]phenyl]hydrazono]-1,3-dioxo-1,3-propanediyl]-dicarbamate (interm. 18).

d) Intermediate (18) (0.0148 mol) was dissolved in acetic acid (75 ml) at RT. Potassium acetate (0.0148 mol) was added and the resulting reaction mixture was stirred and refluxed for 3 hours. The solvent was evaporated, yielding ethyl [[2-[3,5-dichloro-4-[1-[5-[(dimethylamino)methyl]-4-phenyl-2-thiazolyl]-1-methylethyl]phenyl]-2,3,4,5-tetrahydro-3,5-dioxo-1,2,4-triazin-6-yl]carbonyl]carbamate (interm. 19).

e) A solution of intermediate (19) (0.0148 mol) in acetic acid (75 ml) and concentrated HCl (30 ml) was stirred and refluxed overnight. The solvent was evaporated, yielding 2-[3,5-dichloro-4-[1-[5-[(dimethylamino)methyl]-4-phenyl-2-thiazolyl]-1-methylethyl]-phenyl]-2,3,4,5-tetrahydro-3,5-dioxo-1,2,4-triazine-6-carboxylic acid (interm. 20).

Example A4

a) NaOCH_3 30% (0.592 mol) was added to a solution of hydroxylamine hydrochloride (0.1085 mol) in CH_3OH (200 ml), stirred at RT. The mixture was stirred for 10 minutes. Intermediate (3) (0.0542 mol) was added portionwise and the resulting reaction mixture was stirred and refluxed overnight. The solvent was evaporated. The residue was partitioned between CH_2Cl_2 and water. The organic layer was separated, dried, filtered and the solvent was evaporated. The residue was stirred in DIPE, filtered off, washed with DIPE, and dried; yielding 3.7 g of (26%):4-amino-2,6-dichloro- N^{\prime} -hydroxy- α,α -dimethylbenzeneethanimidamide (interm. 21).

b) A solution of intermediate (21) (0.0323 mol) and N,N -bis(methylethyl)ethanamine (0.0339 mol) in CH_2Cl_2 (190 ml) was stirred at 15°C. A solution of 2-chlorobenzoyl chloride (0.0323 mol) in CH_2Cl_2 (10 ml) was added dropwise and the resulting reaction mixture was stirred for one hour. Water was added. The organic layer was separated, dried, filtered and the solvent was evaporated. Toluene was added and azeotroped on the rotary evaporator, yielding 13.0 g of [1-amino-2-(4-amino-2,6-dichlorophenyl)-2-methylpropylidenyl]amino 2-chlorobenzoate (interm. 22).

c) A solution of intermediate (22) (0.0323 mol) and *p*-toluenesulfonic acid (0.0323 mol) in DMSO (100 ml) was stirred for 30 minutes at 150°C. The reaction mixture was cooled. Water was added and this mixture was extracted with toluene. The separated organic layer was dried, filtered and the solvent evaporated. The residue was purified by

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short column chromatography over silica gel (eluent: CH_2Cl_2). The desired fractions were collected and the solvent was evaporated. The concentrate was co-evaporated with EtOAc, yielding 11.7 g of 3,5-dichloro-4-[1-[5-(2-chlorophenyl)-1,2,4-oxadiazol-3-yl]-1-methylethyl]benzenamine (interm. 23).

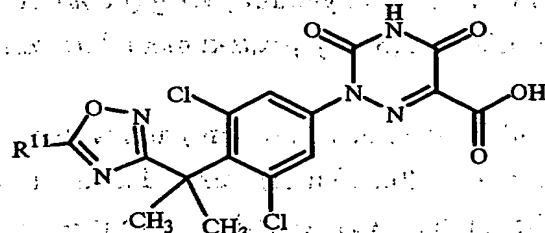
5 d) A solution of intermediate (23) (0.0302 mol) and HCl conc. (0.0906 mol) in acetic acid (100 ml) was stirred at 0°C. A solution of NaNO₂ (0.032 mol) in water (10 ml) was added dropwise at 0°C. The reaction mixture was stirred for 1 hour at 0°C. A powdered mixture of sodium acetate (0.0906 mol) and diethyl(1,3-dioxo-1,3-propanediyl)biscarbamate (0.0332 mol) was added portionwise. The mixture was 10 allowed to warm to RT and stirred for 1 hour. Water was added and this mixture was extracted with CH_2Cl_2 . The separated organic layer was dried, filtered and the solvent evaporated, yielding diethyl N,N' -[2-[3,5-dichloro-4-[1-[5-(2-chlorophenyl)-1,2,4-oxadiazol-3-yl]-1-methylethyl]phenyl]hydrazone]-1,3-dioxo-1,3-propanediyl]dicarbamate (interm. 24).

15 e) A solution of intermediate (24) (0.0302 mol) and sodium acetate (0.0302 mol) in acetic acid (200 ml) was stirred and refluxed for 3 hours. The reaction mixture was poured out into water and this mixture was extracted with CH_2Cl_2 . The separated organic layer was dried, filtered and the solvent evaporated. Toluene was added and azeotroped on the rotary evaporator, yielding ethyl [[2-[3,5-dichloro-4-[1-[5-(2-chlorophenyl)-1,2,4-oxadiazol-3-yl]-1-methylethyl]phenyl]-2,3,4,5-tetrahydro-3,5-dioxo-1,2,4-triazin-6-yl]carbonyl]carbamate (interm. 25).

20 f) A mixture of intermediate (25) (0.0302 mol) in HCl 36% (10 ml) and acetic acid (200 ml) was stirred and refluxed overnight. The reaction mixture was poured out onto crushed ice and this mixture was extracted with CH_2Cl_2 . The separated organic layer was dried, filtered and the solvent evaporated, yielding 16.3 g of 2-[3,5-dichloro-4-[1-[5-(2-chlorophenyl)-1,2,4-oxadiazol-3-yl]-1-methylethyl]phenyl]-2,3,4,5-tetrahydro-3,5-dioxo-1,2,4-triazine-6-carboxylic acid (interm. 26).

30 The following intermediates were prepared analogous to the reaction procedure described in example A.4.

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Table 1

Int. No.	R ¹¹
27	phenyl
28	3-fluoro-phenyl
29	3-chloro-phenyl
30	3-methyl-phenyl
31	3-thienyl
32	2-fluoro-phenyl
33	2-methyl-phenyl
34	4-fluoro-phenyl
35	4-pyridinyl

5

10 Example A5

SOCl₂ (10 ml) was added to a solution of compound (19) (0.00669 mol) in CH₂Cl₂ (30 ml). The reaction solution was stirred and refluxed for 1 hour, then cooled and the solvent was evaporated. Toluene was added and azeotroped on the rotary evaporator, yielding 2-[1-[2,6-dichloro-4-(4,5-dihydro-3,5-dioxo-1,2,4-triazin-2(3H)-yl)phenyl]-1-methylethyl]-4-phenyl-5-thiazoleacetyl chloride (interm. 36).

Example A6

a) A mixture of compound (56) (0.0163 mol) in SOCl₂ (50 ml) and CH₂Cl₂ (50 ml) was stirred at RT for about 3 hours. The solvent was evaporated and the residue was co-evaporated with toluene, yielding 11.3 g of 3-[2-[1-[2,6-dichloro-4-(4,5-dihydro-3,5-dioxo-1,2,4-triazin-2(3H)-yl)phenyl]-1-methylethyl]-4-(2-chlorophenyl)-5-thiazolyl]-benzoyl chloride (interm. 37).

b) Reaction under N₂ atmosphere. 2-Methoxyethanamine (0.0020 mol) was added to a solution of compound (67) (0.001667 mol) in CH₂Cl₂ (25 ml) with MgSO₄ (0.800 g), stirred at RT. The reaction mixture was stirred for 3 days at RT. More 2-methoxyethanamine (2 equiv) was added and the reaction mixture was stirred overnight. MgSO₄ was removed by filtration and the filtrate containing 2-[3,5-dichloro-4-[1-[4-(2-chlorophenyl)-5-[3-[(2-methoxyethyl)imino]methyl]phenyl]-2-thiazolyl]-1-methylethyl]-phenyl]-1,2,4-triazine-3,5(2H,4H)-dione (interm. 38) was used as such in the subsequent reaction step.

30 Example A7

a) A mixture of intermediate (14) (0.0308 mol) in acetic acid (120 ml) and H₂SO₄ (80 ml) was heated to 110°C and stirred for 1.5 hours. The reaction mixture was

allowed to cool to RT and poured out onto crushed ice. The precipitate was filtered off, washed, dissolved in $\text{CH}_2\text{Cl}_2/\text{CH}_3\text{OH}$ 90/10, dried, filtered and the solvent was evaporated. The residue was co-evaporated with toluene, yielding 9.1 g (86%) of 2,6-dichloro-4-(4,5-dihydro-3,5-dioxo-1,2,4-triazin-2(3H)-yl)- α,α -dimethylbenzene-acetamide (interm. 39).

5 b) A mixture of intermediate (39) (0.026 mol) in acetonitrile (180 ml) and water (180 ml) was stirred at RT, (diacetoxido)benzene (0.029 mol) was added and the reaction mixture was stirred for 4 hours. The mixture was poured out into ice-water (400 ml). HCl (20 ml) was added dropwise. The reaction mixture was stirred for 30 minutes and washed with DIPE. The aqueous layer was basified with NaOH 50% and the solvent was evaporated. The residue was extracted with EtOAc and then with $\text{CH}_3\text{OH}/\text{CH}_2\text{Cl}_2$ 90/10. The combined organic layers were dried, filtered and the solvent was evaporated. The residue was co-evaporated with toluene and dried, yielding 6.2 g (75%) of 2-[4-(1-amino-1-methylethyl)-3,5-dichlorophenyl]-1,2,4-triazine-3,5(2H,4H)-dione (interm. 40).

10 c) A mixture of intermediate (40) (0.0032 mol) in tetrahydrofuran (5 ml) was stirred at RT. A solution of benzoyl isothiocyanate (0.0035 mol) in THF (25 ml) was added dropwise at RT and the reaction mixture was stirred for 3 hours. The solvent was removed and the residue was dissolved in CH_2Cl_2 and washed with H_2O . The separated 15 organic layer was dried, filtered and the solvent was evaporated, yielding 1.5 g of N -[[[1-[4-(4,5-dihydro-3,5-dioxo-1,2,4-triazin-2(3H)-yl)-2,6-dichlorophenyl]-1-methyl-ethyl]amino]thioxomethyl]benzamide (interm. 41).

Example A8

20 A mixture of compound (50) (0.0018 mol) in toluene (40 ml) was stirred and heated to 60°C. The mixture was treated with HCl gas for 3 hours and heated to reflux. 25 temperature. Then, the mixture was treated with phosgene gas for 4 hours. N_2 gas was bubbled through the reaction mixture for 1 hour. The solvent was evaporated, yielding 2-[3,5-dichloro-4-[1-methyl-1-[5-(3-nitrosophenyl)-4-phenyl-2-thiazolyl]ethyl]phenyl]-1,2,4-triazine-3,5(2H,4H)-dione (interm. 42).

30 Example A9

a) A mixture of α -(4-amino-2,6-dichlorophenyl)-2-pyridineacetonitrile (0.324 mol) in H_2SO_4 90 % (900ml) was stirred at 90°C for 2 hours, then poured out on ice and basified with a concentrated NH_4OH solution. The precipitate was filtered off, washed with H_2O and centrifuged. The residue was dried, yielding 86.0g (90%) of α -(4-amino-2,6-dichlorophenyl)-2-pyridineacetamide (interm. 43).

35 b) Starting from intermediate 43 and using the same reaction procedures as described in example A2a) through A2c), 2-[4-[(2-pyridinyl)(aminocarbonyl)methyl]-3,5-dichloro-

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phenyl]-2,3,4,5-tetrahydro-3,5-dioxo-1,2,4-triazine-6-carboxylic acid (interm. 44) was prepared.

Example A10

a) A mixture of (\pm) -2,6-dichloro- α -methyl-4-nitrobenzeneacetonitrile (0.1632 mol) in a mixture of H_2SO_4/H_2O /acetic acid (150 ml) was stirred and refluxed for 2 hours, then poured out onto crushed ice and this mixture was extracted with CH_2Cl_2 . The separated organic layer was dried, filtered and the solvent evaporated. The residue was purified by short column chromatography over silica gel (eluent: CH_2Cl_2/CH_3OH 98/2). The desired fractions were collected and the solvent was evaporated, yielding 31.9 g (74%) of 2,6-dichloro- α -methyl-4-nitrobenzeneacetic acid (interm. 45).

b) A solution of intermediate (45) (0.0756 mol) in $SOCl_2$ (200 ml) was stirred and refluxed for 2 hours. The solvent was evaporated. Toluene was added and azeotroped on the rotary evaporator, yielding 2,6-dichloro- α -methyl-4-nitrobenzeneacetyl chloride (interm. 46).

c) A solution of intermediate (46) (0.0756 mol) in CH_2Cl_2 (50 ml) was added to a solution of benzoylhydrazine (0.0756 mol) and *N,N*-(1-methylethyl)ethaneamine (0.0832 mol) in CH_2Cl_2 (250 ml), stirred at 0 °C. The reaction mixture was stirred for one hour at RT. Water was added. The organic layer was separated, dried, filtered and the solvent was evaporated. The residue was purified by short column chromatography over silica gel (eluent: CH_2Cl_2/CH_3OH 97/3). The desired fractions were collected and the solvent was evaporated. The residue was stirred in diethyl ether, filtered off, washed with diethyl ether and dried, yielding 27.5 g (95%) of [2-[2-(2,6-dichloro-4-nitrophenyl)-1-oxopropyl]hydrazide]benzenecarboxylic acid (interm. 47).

d) A mixture of intermediate (47) (0.072 mol) in $POCl_3$ (250 ml) was stirred overnight at RT. The solvent was evaporated. Toluene was added and azeotroped on the rotary evaporator. The residue was taken up into CH_2Cl_2 , washed with a 10% aqueous $NaHCO_3$ solution, dried, filtered and the solvent was evaporated. The residue was crystallized from diethyl ether, filtered off, washed with diethyl ether and dried in vacuo, yielding 20.1 g (77%) of 2-[1-(2,6-dichloro-4-nitrophenyl)ethyl]-5-phenyl-1,3,4-oxodiazole (interm. 48).

e) A mixture of intermediate (48) (0.023 mol) in CH_3OH (150 ml) was hydrogenated with palladium on activated charcoal (5%) (2 g) as a catalyst in the presence of thiophene (2 ml). After uptake of hydrogen (3 equiv), the catalyst was filtered off over dicalite and the filtrate was evaporated. The residue was crystallized from diethyl ether, filtered off, washed with diethyl ether and dried, yielding 5 g (65%) of 3,5-dichloro-4-[1-(5-phenyl-1,3,4-oxodiazol-2-yl)ethyl]benzenearmine (interm. 49).

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B. Preparation of the final compounds

Example B1

a) A mixture of intermediate (10) (0.0133 mol) in mercaptoacetic acid (7ml) was stirred at 175°C for 2 hours. The mixture was cooled, poured out into ice water, basified with 5 K_2CO_3 and extracted with EtOAc. The organic layer was separated, washed with H_2O , dried, filtered and the solvent was evaporated. The residue was purified by column chromatography over silica gel (eluent: CH_2Cl_2/CH_3OH 99/1). The pure fractions were collected and the solvent was evaporated, yielding 2.2g (36%) of 2-[3,5-dichloro-4-[1-methyl-1-(4-phenyl-2-thiazolyl)ethyl]phenyl]-1,2,4-triazine-3,5(2H,4H)-dione (comp. 1).

b) A mixture of intermediate (44) (0.00958 mol) in mercaptoacetic acid (30ml) was stirred at 175°C for 3 hours and then allowed to cool to RT. CH_2Cl_2 and ice was added. Then K_2CO_3 10% was added. The organic layer was separated, dried, filtered and the solvent was evaporated. The residue was purified by column chromatography over silica 15 gel (eluent: CH_2Cl_2/CH_3OH 97/3). The pure fractions were collected and the solvent was evaporated. The residue was taken up in K_2CO_3 10%. The mixture was washed with CH_2Cl_2 and acidified with HCl 6N. The precipitate was filtered off, washed with 2-propanone and dried, yielding 0.4g of 2-[3,5-dichloro-4-(2-pyridinylmethyl)phenyl]-1,2,4-triazine-3,5(2H,4H)-dione hydrochloride(1:1); hydrate(1:1) (comp. 107).

Example B2

A solution of intermediate (15) (0.0111 mol) and 2-bromo-1-(3-chlorophenyl)-1-propanone (0.0121 mol) in ethanol (40 ml) and DMF (40 ml) was stirred for 4 hours at 20 80°C. The solvent was evaporated. Toluene was added and azeotroped on the rotary evaporator. The crude oil was stirred in CH_2Cl_2 , washed with water, dried, filtered and the solvent was evaporated. The residue was crystallized from EtOAc. The precipitate 25 was filtered off, washed with EtOAc, and dried, yielding 4.3 g (76%) of 2-[3,5-di-chloro-4-[1-[4-(3-chlorophenyl)-5-methyl-2-thiazolyl]-1-methylethyl]phenyl]-1,2,4-triazine-3,5(2H,4H)-dione (comp. 3).

Example B3

30 a) A mixture of compound (9) (0.00183 mol) and NaOH 1N (0.0055 mol) in CH_3OH (25 ml) and THF (25 ml) was stirred overnight at RT. The reaction mixture was acidified with 1N HCl (8 ml), and the product was taken up into EtOAc. The organic layer was washed with brine, dried, filtered and the solvent was evaporated. The residue was crystallized from CH_3CN . The precipitate was filtered off, washed with DIPE, and dried, yielding 0.8 g (79%) of 2-[1-[2,6-dichloro-4-(4,5-dihydro-3,5-dioxo-1,2,4-triazin-2(3H)-yl)phenyl]-1-methylethyl]-4-phenyl-5-thiazoleacetic acid (comp. 19).

b) A mixture of compound (19) (0.00483 mol), 1,4'-bipiperidine dihydrochloride (0.0058 mol) and *N*-ethyl-*N*-(1-methylethyl)-2-propanamine (0.0145 mol) in CH₂Cl₂ (50 ml) was stirred and cooled to 0°C under N₂ atmosphere. *N*'-(ethylcarbonimidoyl)-*N,N*-dimethyl-1,3-propanediamine monohydrochloride (0.0058 mol) was added at 0°C.

5 The mixture was allowed to warm to RT, then stirred overnight. Water was added and this mixture was extracted with CH₂Cl₂/CH₃OH (9:1). The separated organic layer was dried, filtered and the solvent evaporated. The residue was purified by column chromatography over silica gel (eluent: CH₂Cl₂/CH₃OH 92.5/7.5). The desired fractions were collected and the solvent was evaporated. The residue was further 10 purified by HPLC over silica gel (eluent: CH₂Cl₂/CH₃OH gradient from 100/0 to 90/10 in 30 min). The desired fractions were collected and the solvent was evaporated. The residue was stirred in boiling DIPE, then filtered off and dried, yielding 1.0 g (33%) of 1'-[[2-[1-[2,6-dichloro-4-(4,5-dihydro-3,5-dioxo-1,2,4-triazin-2(3H)-yl)phenyl]-1-methylethyl-4-phenyl-5-thiazolyl]acetyl]-1,4'-dipiperidine (comp. 24).

15 Example B4

A solution of intermediate (36) (0.00334 mol) in CH₂Cl₂ (20 ml) was stirred at RT. *N,N*-bis(1-methylethyl)ethanamine (0.00668 mol) was added. A solution of 1-(phenylmethyl)piperazine (0.0067 mol) in CH₂Cl₂ (10 ml) was added slowly at 0°C. The reaction mixture was stirred overnight at RT. CH₂Cl₂ was added. Brine was added. The 20 organic layer was separated, dried, filtered and the solvent was evaporated. The residue was purified by HPLC over silica gel (eluent: CH₂Cl₂/CH₃OH from 100/0 to 90/10 in 30 minutes). The pure fractions were collected and the solvent was evaporated. The residue was stirred in DIPE, filtered off and dried, yielding 0.3 g (15%) of 1'-[[2-[1-[2,6-dichloro-4-(4,5-dihydro-3,5-dioxo-1,2,4-triazin-2(3H)-yl)phenyl]-1-methylethyl]-4-phenyl-2-thiazolyl]acetyl-4-phenylmethyl)piperazine (comp. 35).

Example B5

Sodium (0.0067 mol) was dissolved in ethanol (8ml) at 0°C under N₂ flow and then added dropwise at RT under N₂ flow to a stirring solution of compound (25) (0.0067 mol) in THF (40ml). The mixture was heated to reflux temperature. NaBH₄ 30 (0.010 mol) was added portionwise. The mixture was stirred for 30 minutes, then cooled to RT, poured out into ice water, acidified with a concentrated HCl solution and extracted with CH₂Cl₂. The organic layer was separated, washed with H₂O, dried, filtered and the solvent was evaporated. The residue was crystallized from ethanol. The precipitate was filtered off, washed with DIPE and dried, yielding 3.7g (99%) of 35 (±)-2-[3,5-dichloro-4-[1-[5-(hydroxyphenylmethyl)-4-phenyl-2-thiazolyl]-1-methyl-ethyl]phenyl]-1,2,4-triazin-3,5(2H,4H)-dione (comp. 29).

Example B6

a) A solution of compound (30) (0.00457 mol) in CH_2Cl_2 (60ml) was stirred at RT. BBr_3 1M in CH_2Cl_2 (0.0137 mol) was added dropwise. The mixture was stirred and refluxed for 16 hours, then treated with CH_3OH (15ml) and washed with H_2O . The 5 organic layer was separated, dried, filtered and the solvent was evaporated, yielding 2.1g of (84%) 2-[4-[1-[5-(bromomethyl)-4-phenyl-2-thiazolyl]-1-methylethyl]-3,5-dichlorophenyl]-1,2,4-triazine-3,5(2H,4H)-dione (comp. 41).

b) A mixture of compound (41) (0.0018 mol), 1-(methoxyethyl)piperazine (0.0018 mol) and K_2CO_3 (0.0036 mol) in CH_3CN (50ml) was stirred and refluxed for 16 hours. The 10 solvent was evaporated and the residue was dissolved in CH_2Cl_2 and washed with H_2O . The organic layer was dried, filtered and the solvent was evaporated. The residue was purified by flash chromatography over silica gel (eluent: $\text{CH}_2\text{Cl}_2/\text{CH}_3\text{OH}$ 99.8/0.2, 99/1 and 95/5). The desired fractions were collected and the solvent was evaporated. The residue was stirred in DIPE. The precipitate was filtered off, washed and dried, yielding 15 0.6g (55%) of 2-[3,5-dichloro-4-[1-[5-[4-(2-methoxyethyl)-1-piperazinyl]methyl]-4-phenyl-2-thiazolyl]-1-methylethyl]phenyl]-1,2,4-triazine-3,5(2H,4H)-dione (comp. 42).

Example B7

a) A mixture of compound (49) (0.036 mol) in THF (300 ml) was hydrogenated at 50°C with Pt/C 5% (3 g) as a catalyst in the presence of thiophene (3 ml). After partial 20 uptake of H_2 , the catalyst was filtered off and the filtrate was concentrated. The residual fraction was hydrogenated again with Pt/C 5% (5 g) as a catalyst. After uptake of H_2 , the catalyst was filtered off and the filtrate was evaporated. The residue was purified by HPLC over silica gel (eluent: $\text{CH}_2\text{Cl}_2/\text{CH}_3\text{OH}$ 98/2). The desired fractions were collected and their solvent was evaporated. The residue was stirred in DIPE, 25 filtered off, washed and dried, yielding 11 g of 2-[4-[1-[5-(3-aminophenyl)-4-phenyl-2-thiazolyl]-1-methylethyl]-3,5-dichlorophenyl]-1,2,4-triazine-3,5(2H,4H)-dione (comp. 50).

b) A mixture of compound (50) (0.0018 mol), acetic acid anhydride (0.0024 mol) and N,N -dimethyl-4-pyridinamine (0.0021 mol) in CH_2Cl_2 (15 ml) was stirred for 30 minutes 30 at RT. More CH_2Cl_2 was added and the resulting solution was washed with a 5% aqueous NaHCO_3 solution, with 1N HCl and with water, dried, filtered and the solvent was evaporated. The residue was purified by flash column chromatography over silica gel (eluent: $\text{CH}_2\text{Cl}_2/\text{CH}_3\text{OH}$ 99.8/0.2 up to 98/2). The desired fractions were collected and the solvent was evaporated. The residue was stirred in DIPE, filtered off and dried, 35 yielding 0.7 g (65%) of N -[3-[2-[1-[2,6-dichloro-4-(4,5-dihydro-3,5-dioxo-1,2,4-triazin-2(3H)-yl)phenyl]-1-methylethyl]-4-phenyl-5-thiazolyl]phenyl]acetamide (comp. 51).

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c) A mixture of compound (50) (0.0018 mol) and cyanic acid sodium salt (0.0117 mol) in acetic acid (30 ml) and water (60 ml) was stirred for two days at 40°C. The solvent was evaporated. The residue was taken up into water. This mixture was extracted with CH₂Cl₂/CH₃OH (90/10). The organic layer was separated, dried, filtered and the solvent was evaporated. The residue was dissolved in acetic acid (50 ml) and H₂O (5 ml). The resulting suspension was stirred for 2 hours at 60°C. The solution was allowed to cool to RT, then concentrated. The residue was taken up into water, then extracted with CH₂Cl₂/CH₃OH (90/10). The separated organic layer was dried, filtered and the solvent evaporated. The residue was purified by HPLC over silica gel (eluent: CH₂Cl₂/CH₃OH 100/0, 90/10 (30 minutes)). The pure fractions were collected and the solvent was evaporated. The residue was stirred in DIPE, filtered off, washed and dried, yielding 0.5 g of *N*-[3-[2-[1-[2,6-dichloro-4-(4,5-dihydro-3,5-dioxo-1,2,4-triazin-2(3H)-yl)phenyl]-1-methylethyl]-4-phenyl-5-thiazolyl]phenyl]urea (comp. 54).

d) A solution of compound (50) (0.0009 mol) and *N,N*-bis(1-methylethyl)ethanamine (0.0013 mol) in CH₂Cl₂ (20 ml) was stirred and cooled to 0-5°C. A solution of sulfamoyl chloride (0.0013 mol) in CH₂Cl₂ (10 ml) was added dropwise at 0°C. The reaction mixture was stirred for another 2 hours and H₂O (20 ml) was added. The separated organic layer was dried, filtered and the solvent was evaporated. The residue was purified by HPLC over Kromasil C18 (eluent: (0.5% ammonium acetate in H₂O)/CH₃OH/CH₃CN 67.5/25/7.5; after 10 minutes 0/50/50). The pure fractions were collected and the solvent was evaporated. The residue was stirred in DIPE. The precipitate was filtered off, washed and dried, yielding 0.3 g of *N*-[3-[2-[1-[2,6-dichloro-4-(4,5-dihydro-3,5-dioxo-1,2,4-triazin-2(3H)-yl)phenyl]-1-methylethyl]-4-phenyl-5-thiazolyl]phenyl]sulfamide (comp. 60).

e) A mixture of compound (50) (0.00227 mol) and D-glucose (0.750 g) in ethanol (50 ml) and DMF (25 ml) was stirred overnight at 100°C under N₂ atmosphere. More D-glucose (0.200 g) was added and the reaction mixture was stirred for 3 hours at 100°C. The solvent was evaporated. The residue was purified by HPLC (eluent: (0.5% ammonium acetate in H₂O)/CH₃OH/CH₃CN 40/30/30). The desired fractions were collected and the solvent was evaporated. CH₃CN was added to the oil and precipitation resulted. The residues were repurified by column chromatography over silica gel (eluent: CH₂Cl₂/CH₃OH from 90/10 to 0/100). The desired fractions were collected and the solvent was evaporated. The residue was stirred in DIPE, filtered off, dried, yielding 0.5 g (31%) of (α + β)-2-[3,5-dichloro-4-[1-[5-[3-[[tetrahydro-3,4,5,6-tetrahydro-2H-pyran-2-yl]amino]phenyl]-4-phenyl-2-thiazolyl]-1-methylethyl]phenyl]-1,2,4-triazine-3,5(2H,4H)-dione 2-propanolate(1:1) (comp. 64).

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Example B8

a) A solution of compound (55) (0.0137 mol) in acetic acid (90 ml) was stirred at RT. HBr 48% (75 ml) was added and the reaction mixture was stirred overnight at 90°C, then for 7 days at 100°C. More HBr 48% (20 ml) was added and the resulting reaction mixture was poured out into water (600 ml). This mixture was extracted with CH₂Cl₂/CH₃OH 95/5. The precipitate was filtered off from the organic and aqueous layer. The solid was stirred in boiling CH₃CN, then cooled to RT. The precipitate was filtered off and dried, washed with DIPE and dried. The product was stirred in CH₂Cl₂/CH₃OH 90/10 (100 ml) and a saturated aqueous NaHCO₃ solution (50 ml), filtered off, washed with water, then with CH₂Cl₂/CH₃OH 90/10, and dried, yielding 4.4 g of 2-[3,5-dichloro-4-[1-[5-(3-hydroxyphenyl)-4-phenyl-2-thiazolyl]-1-methylethyl]-phenyl]-1,2,4-triazine-3,5(2H,4H)-dione (comp. 58).

b) A mixture of compound (58) (0.00363 mol) and *N,N*-bis(1-methylethyl)ethanamine (0.00718 mol) in CH₂Cl₂ (40 ml) was stirred at 0-5°C under N₂ atmosphere. A mixture of sulfamoyl chloride (0.00508 mol) in CH₂Cl₂, (20 ml) was added in one portion. The resulting reaction mixture was stirred for 1 hour at 0°C, then stirred overnight at RT. More sulfamoyl chloride (0.3 g) was added and the reaction mixture was stirred for 2 hours at 40°C, then stirred further overnight. Water was added. CH₂Cl₂/CH₃OH 95/5 was added and the layers were separated. The organic layer was separated, washed with water, dried, filtered and the solvent was evaporated. The residue was purified by HPLC over silica gel (eluent: CH₂Cl₂/CH₃OH 100/0 to 97/3 over 30 minutes), then over RP-18 BDS (eluent: (0.5% ammonium acetate in H₂O)/CH₃OH/CH₃CN 36/32/32, then 8/46/46 and finally 0/0/100). The desired fractions were collected and the solvent was evaporated, yielding 0.5 g of 3-[2-[1-[2,6-dichloro-4-(4,5-dihydro-3,5-dioxo-1,2,4-triazin-2(3H)-yl)phenyl]-1-methylethyl]-4-phenyl-5-thiazolyl]phenylsulfamate (ester) (comp. 66).

Example B9

a) A solution of intermediate (37) (0.0163 mol) in 1,4-dioxane (125 ml) was stirred at RT under N₂ flow. NaBH₄ (0.0815 mol) was added portionwise. More NaBH₄ (0.0264 mol) was added portionwise and the reaction mixture was stirred at RT overnight. HCl 1N (80 ml) was added dropwise till a pH of about 4. The mixture was poured out into water (200 ml) and extracted with CH₂Cl₂. The organic layer was washed with water, dried, filtered and the solvent was evaporated. The residue was purified by flash column chromatography over silica gel (eluent: CH₂Cl₂/CH₃OH 99/1, then 98/2 and finally 95/5). The desired fractions were collected and the solvent was evaporated. The residue was co-evaporated with EtOAc, then crystallized from CH₃CN. The precipitate was filtered off, washed with DIPE and dried, yielding 5.0 g of 2-[3,5-dichloro-4-[1-[4-

(2-chlorophenyl)-5-[3-(hydroxymethyl)phenyl]-2-thiazolyl]-1-methylethyl]phenyl]-1,2,4-triazine-3,5(2H,4H)-dione (comp. 59).

b) MnO_2 (0.008335 mol) was added portionwise to a solution of compound (59) (0.001667 mol) in CH_2Cl_2 (15 ml). The mixture was stirred for 1 hour. More MnO_2 (0.008335 mol) was added and the reaction mixture was stirred again for 1 hour, then heated to 50°C and stirred overnight at 50°C. The reaction mixture was cooled, filtered over dicalite and the filtrate was evaporated, yielding 3-[2-[1-[2,6-dichloro-4-(4,5-dihydro-3,5-dioxo-1,2,4-triazin-2(3H)-yl)phenyl]-1-methylethyl]-4-(2-chlorophenyl)-5-thiazolyl]benzaldehyde (comp. 67).

c) A mixture of intermediate (38) (0.000305 mol) and $\text{NaB}(\text{OAc})_3\text{H}$ (0.000458 mol) in 1,2-dichloroethane (3.0 ml) was stirred at RT under N_2 atmosphere. Acetic acid (1.0 ml) was added dropwise and the reaction mixture was stirred over the weekend at RT, yielding 2-[3,5-dichloro-4-[1-[4-(2-chlorophenyl)-5-[3-[(2-methoxyethyl)amino]-methyl]phenyl]-2-thiazolyl]-1-methylethyl]phenyl]-1,2,4-triazine-3,5(2H,4H)-dione (comp. 68).

Example B10

A solution of intermediate (37) (0.00407 mol) in CH_2Cl_2 (40 ml) was stirred at RT under N_2 atmosphere. A solution of 2-methoxyethanamine (0.0122 mol) in CH_2Cl_2 (15 ml) was added dropwise and the reaction mixture was stirred overnight at RT. Water (100 ml) was added. $\text{CH}_2\text{Cl}_2/\text{CH}_3\text{OH}$ 95/5 (100 ml) was added and the biphasic mixture was acidified to a pH of about 5 with 1N HCl. The organic layer was separated, washed with water, dried, filtered and the solvent was evaporated, then co-evaporated with EtOAc. The residue was stirred in boiling 2-methoxy-2-methylpropane, then cooled to RT, filtered off, washed and dried. This fraction was taken up into $\text{CH}_2\text{Cl}_2/\text{CH}_3\text{OH}$ 90/10, washed with half-saturated NaHCO_3 solution, with 1N HCl, with water, then dried, filtered and the solvent was evaporated, then co-evaporated with EtOAc. The residue was stirred in boiling 2-methoxy-2-methylpropane, filtered off while still hot and the filtrate was evaporated. The residue was dried, yielding 0.7 g of 3-[2-[1-[2,6-dichloro-4-(4,5-dihydro-3,5-dioxo-1,2,4-triazin-2(3H)-yl)phenyl]-1-methylethyl]-4-(2-chlorophenyl)-5-thiazolyl]-N-(2-methoxyethyl)benzamide (comp. 63).

Example B11

NH_3 25% (40 ml) was stirred at 0°C. A solution of intermediate 37 (0.00407 mol) in 1,4-dioxane (20 ml) was added dropwise and the resulting reaction mixture was stirred overnight at RT. Concentrated HCl (35 ml) was added dropwise at 0°C. Water (100 ml) was added and this mixture was extracted with $\text{CH}_2\text{Cl}_2/\text{CH}_3\text{OH}$ 95/5 (150 ml). The separated organic layer was washed with water, dried, filtered and the solvent evaporated. EtOAc was added and azeotroped on the rotary evaporator. The residue

was crystallized from 2-propanol. The precipitate was filtered off, washed with 2-propanol and DIPE, and dried, yielding 0.8 g (33%) of 3-[2-[1-[3,5-dichloro-4-(4,5-dihydro-3,5-dioxo-1,2,4-triazin-2(3H)-yl)phenyl]-1-methylethyl]-4-(2-chlorophenyl)-5-thiazolyl]benzamide (comp. 62).

5 **Example B12**

A mixture of intermediate (41) (0.0025 mol) in H₂O (30 ml) was stirred at RT and NaOH 10% (15 ml) was added. The reaction mixture was stirred at 100°C for 45 minutes and acidified at RT with 1N HCl. The precipitate was filtered off, washed with H₂O and dried, yielding 0.5 g of *N*-[1-[2,6-dichloro-4-(4,5-dihydro-3,5-dioxo-1,2,4-triazin-2(3H)-yl)phenyl]-1-methylethyl]thiourea (comp. 99).

10 **Example B13**

A solution of 3-pyridinecarboxylic acid (0.003 mol) and triethyl amine (0.003 mol) in CH₃CN (30 ml) was stirred at RT. Phosphorus(1+), (1-hydroxy-1*H*-benzotriazolato-O)tris(*N*-methylmethanaminato)-, (T-4)-, hexafluorophosphate(1-) (0.003 mol) was

15 added portionwise and the mixture was stirred for 45 minutes. Intermediate 40 (0.003 mol) was added and the resulting reaction mixture was stirred overnight. The solvent was evaporated. The residue was purified by flash column chromatography over silica gel (eluent: CH₂Cl₂/CH₃OH 99.5/0.5 up to 97.5/2.5). The desired fractions were collected and the solvent was evaporated. The residue was stirred in CH₂Cl₂, filtered 20 off, washed and dried, yielding 0.4 g of *N*-[1-[2,6-dichloro-4-(4,5-dihydro-3,5-dioxo-1,2,4-triazin-2(3H)-yl)phenyl]-1-methylethyl]-3-pyridinecarboxamide (comp. 101).

25 **Example B14**

A mixture of compound (56) (0.00407 mol) in CH₂Cl₂, p.a. (30 ml) was stirred at RT under N₂ flow. 1,1'-carbonylbis-1*H*-imidazole (0.00407 mol) was added portionwise and the reaction mixture was stirred at RT for 20 minutes. More 1,1'-carbonylbis-1*H*-imidazole (0.00086 mol) was added and the reaction mixture was stirred further at RT for 30 minutes. A solution of 1-methylpiperazine (0.0122 mol) in CH₂Cl₂ (10 ml) was added dropwise and the reaction mixture was stirred at RT for 1 hour. CH₂Cl₂/CH₃OH 80/20 (50 ml) was added. The organic layer was washed with a half-saturated NaCl

30 solution, separated, dried, filtered, and the solvent was evaporated and then co-evaporated with EtOAc. The residue was purified by flash column chromatography over silica gel (eluent: CH₂Cl₂/CH₃OH 99.5/0.5, 97/3 and 90/10). The desired fractions were collected, and the solvent was evaporated and then co-evaporated with EtOAc. The residue was crystallized from 2-propanol. The precipitate was filtered off, washed with DIPE and dried, yielding 0.7 g (25 %) of 1-[3-[2-[1-[2,6-dichloro-4-(4,5-dihydro-3,5-dioxo-1,2,4-triazin-2(3H)-yl)phenyl]-1-methylethyl]-4-(2-chlorophenyl)-5-thiazolyl]benzoyl]-4-methylpiperazine (comp. 61).

Example B15

a) A solution of intermediate (42) (0.0009 mol) in THF (20 ml) was stirred at RT under N₂ atmosphere. A solution of 1-(phenylmethyl)piperazine (0.0009 mol) in THF (5 ml) was added dropwise. The reaction mixture was stirred overnight at RT. The solvent was evaporated, yielding *N*-[3-[2-[1-[2,6-dichloro-4-(4,5-dihydro-3,5-dioxo-1,2,4-triazin-2(3*H*)-yl)phenyl]-1-methylethyl]-4-phenyl-5-thiazolyl]phenyl]-4-(phenylmethyl)-1-piperazinecarboxamide (comp. 70).

b) 1-chloroethyl chloroformate (0.00117 mol) was added slowly to a solution of compound (70) (0.0009 mol) in CH₂Cl₂ (15 ml), stirred at 0°C. The reaction mixture was stirred for 90 minutes at 0°C. The solvent was evaporated and the residue was dissolved in methanol (30 ml). The mixture was stirred and refluxed for 1 hour. The solvent was evaporated. The residue was purified by flash column chromatography over silica gel (eluent: CH₂Cl₂/CH₃OH 97.5/2.5). The desired fractions were collected and the solvent was evaporated. The residue was further purified by HPLC over RP-18 (BDS; eluent: (0.5% ammonium acetate in H₂O)/CH₃OH/CH₃CN; gradient from 36/32/32 to 8/46/46 in 24 minutes and then to 0/0/100 in 32 minutes). The pure fractions were collected and the solvent was evaporated. The residue was stirred in DIPE, filtered off, washed and dried, yielding 0.1 g of *N*-[3-[2-[1-[2,6-dichloro-4-(4,5-dihydro-3,5-dioxo-1,2,4-triazin-2(3*H*)-yl)phenyl]-1-methylethyl]-4-phenyl-5-thiazolyl]-1-phenyl]-1-piperazinecarboxamide monohydrate (comp. 71).

Example B16

a) A mixture of compound (87) (0.0011 mol), 1-bromo-2,5-pyrrolinedione (0.0011 mol) and dibenzoyl peroxide (catalytic quantity) in CCl₄ (30 ml) was stirred and refluxed for 3 hours. The mixture was allowed to cool to RT. The mixture was filtered over dicalite and the filtrate contained 2-[4-[1-[5-[2-(bromomethyl)phenyl]-1,2,4-oxadiazol-3-yl]-1-methylethyl]-3,5-dichlorophenyl]-1,2,4-triazine-3,5(2*H*,4*H*)-dione (comp 95).

b) A solution of compound (95) (0.0011 mol) in CCl₄ (30 ml) was stirred at RT. 1-Methylpiperazine (0.0033 mol) was added dropwise and the resulting reaction mixture was stirred and refluxed for 1 hour. The solvent was evaporated and the crude residue was filtered over dicalite (eluent: CH₂Cl₂/CH₃OH 97/3, 95/5 and 85/15). The desired fractions were collected and the solvent was evaporated. The residue was dissolved in 2-propanol and converted into the HCl salt (1:3) with HCl/2-propanol. The precipitate was filtered off, washed, and dried, yielding 0.3 g of 2-[3,5-dichloro-4-[1-methyl-1-[5-[2-[(4-methyl-1-piperazinyl)methyl]phenyl]-1,2,4-oxadiazol-3-yl]ethyl]phenyl]-1,2,4-triazine-3,5(2*H*,4*H*)-dione trihydrochloride (comp. 94).

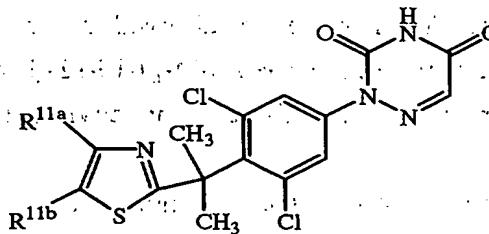
Example B17

a) A mixture of compound (74) (0.0049 mol) in CH_3OH (100ml) and THF (30ml) was hydrogenated at RT under a 3 bar pressure for 3 hours with Raney Nickel (2.5g) as a catalyst. After uptake of H_2 , the catalyst was filtered through celite, washed with CH_3OH and THF and the filtrate was evaporated. The residue (1.5g) was purified by column chromatography over silica gel (eluent: $\text{CH}_2\text{Cl}_2/\text{CH}_3\text{OH}$ 97/3). The pure fractions were collected and the solvent was evaporated, yielding 1.3g (53%) of 2-[4-[1-[4-(5-amino-2-thienyl)-2-thiazolyl]-1-methylethyl]-3,5-dichlorophenyl]-1,2,4-triazine-3,5(2H,4H)-dione (comp. 80).

b) Methanesulfonyl chloride (0.0044 mol) was added dropwise at 10°C under N_2 flow to a solution of compound (80) (0.00208 mol) and *N,N*-bis(1-methylethyl)ethanamine (0.0062 mol) in CH_2Cl_2 (20ml). The mixture was stirred at RT for 12 hours, then poured out into H_2O and decanted. The organic layer was washed with H_2O , dried, filtered and the solvent was evaporated. The residue was purified by column chromatography over silica gel (eluent: $\text{CH}_2\text{Cl}_2/\text{CH}_3\text{OH}$ 98/2). The pure fractions were collected and the solvent was evaporated. The residue was crystallized from 2-propanone and diethyl ether. The precipitate was filtered off and dried, yielding 0.2g (18%) of *N*-[5-[2-[1-[2,6-dichloro-4-(4,5-dihydro-3,5-dioxo-1,2,4-triazine-2(3H)-yl)phenyl]-1-methylethyl]-4-thiazolyl]-2-thienyl]-*N*-(methylsulfonyl)methanesulfonamide (comp. 81).

20

The following tables list compounds of formula (I) which were prepared according to one of the above examples.

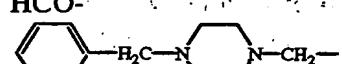
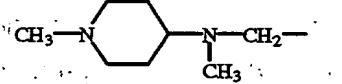
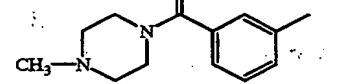
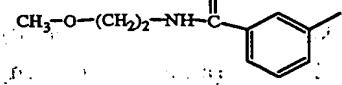
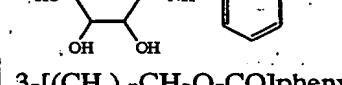
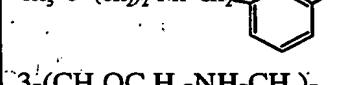
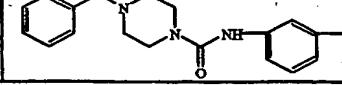
Table 2

Co. No.	Ex. No.	R^{11a}	R^{11b}	Salt / melting point
1	B.1a	phenyl	H	mp. 120°C
2	B.1a	phenyl	$(\text{CH}_3)_2\text{N}-\text{CH}_2-$	HCl (1:1)
3	B.2	3-chlorophenyl	CH_3	
4	B.2	2-chlorophenyl	H	
5	B.2	2-thienyl	H	
6	B.2	phenyl	$\text{C}_2\text{H}_5-\text{O}-\text{CO}-$	
7	B.2	4-pyridinyl	H	
8	B.2	3-chlorophenyl	H	
9	B.2	phenyl	$\text{C}_2\text{H}_5-\text{O}-\text{CO}-\text{CH}_3$	

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Co. No.	Ex. No.	R ^{11a}	R ^{11b}	Salt / melting point
10	B.2	phenyl	CH ₃	
11	B.2	2-fluorophenyl	H	
12	B.2	4-bromophenyl	H	
13	B.2	2,6-difluorophenyl	H	
14	B.2	phenyl	4-morpholinyl	
15	B.2	2-fluorophenyl	CH ₃	
16	B.2	phenyl	1-methyl-4-piperazinyl	
17	B.2	3-fluorophenyl	CH ₃	
18	B.2	2,4-difluorophenyl	H	
19	B.3a	phenyl	HOOC-CH ₂ -	
20	B.3b	phenyl	4-morpholinyl-CO-CH ₂ -	
21	B.3b	phenyl		
22	B.3b	phenyl		
23	B.2	phenyl	phenyl	
24	B.3b	phenyl		
25	B.2	phenyl	phenyl-CO-	
26	B.2	2-methoxyphenyl	H	
27	B.2	2-chlorophenyl	CH ₃	
28	B.2	3-fluorophenyl	H	
29	B.5	phenyl	phenyl-CH(OH)-	
30	B.2	phenyl	CH ₃ -O-CH ₂ -	
31	B.2	CH ₃	phenyl	
32	B.2	2-chlorophenyl	phenyl	
33	B.2	phenyl	3-pyridinyl	
34	B.2	2-fluorophenyl	phenyl	
35	B.4	phenyl		
36	B.3b	phenyl		
37	B.2	3-chlorophenyl	phenyl	
38	B.2	2-methylphenyl	phenyl	
39	B.2	phenyl	1-(CH ₃ -CO)-4-piperidinyl-	
40	B.2	2-methylphenyl	H	
41	B.6a	phenyl	Br-CH ₂ -	
42	B.6b	phenyl		
43	B.2	phenyl	phenylmethyl	

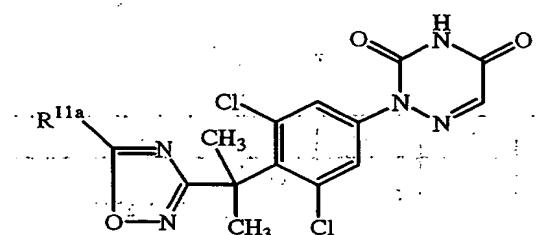
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Co. No.	Ex. No.	R ^{11a}	R ^{11b}	Salt / melting point
44	B.2	3-(CH ₃ OCH ₂)phenyl	CH ₃ -	
45	B.2	phenyl	phenylethyl	
46	B.2	2-chlorophenyl	HCO-	
47	B.6b	phenyl		HCl (1:2); H ₂ O (1:1)
48	B.2	4-phenylphenyl-	C ₂ H ₅ -	
49	B.2	phenyl	3-(NO ₂)-phenyl	
50	B.7a	phenyl	3-(NH ₂)-phenyl	
51	B.7b	phenyl	3-(CH ₃ -CO-NH)-phenyl	
52	B.6b	phenyl		acetate (1:2)
53	B.6b	phenyl		acetate (2:1)
54	B.7c	phenyl	3-(H ₂ N-CO-NH)-phenyl-	
55	B.2	phenyl	3-methoxyphenyl	
56	B.2	2-chlorophenyl	3-HOOC-phenyl	
57	B.2	2-chlorophenyl	3-CN-phenyl	
58	B.8a	phenyl	3-OH-phenyl	
59	B.9a	2-chlorophenyl	3-(HO-CH ₂)-phenyl-	
60	B.7d	phenyl	3-(NH ₂ -SO ₂ -NH)-phenyl-	
61	B.14	2-chlorophenyl		
62	B.11	2-chlorophenyl	3-(H ₂ N-CO)-phenyl-	
63	B.10	2-chlorophenyl		
64	B.7e	phenyl		2-propanolate (1:1)
65	B.2	2-chlorophenyl	3-[(CH ₃) ₂ -CH-O-CO]phenyl	
66	B.8b	phenyl	3-(NH ₂ -SO ₂ -O)phenyl	
67	B.9b	2-chlorophenyl	3-HCO-phenyl	
68	B.9e	2-chlorophenyl		
69	B.9c	2-chlorophenyl	3-(CH ₃ OCH ₂ H ₅ -NH-CH ₂)-phenyl	HCl (1:1)
70	B.15a	phenyl		

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Co. No.	Ex. No.	R^{11a}	R^{11b}	Salt / melting point
71	B.15b	phenyl		H_2O (1:1)
72	B.2	3-thienyl	H	mp. 115°C
73	B.2	5-chloro-2-thienyl	H	mp. 220°C
74	B.2	5-nitro-2-thienyl	H	mp. 235°C
75	B.2	3-methyl-2-thienyl	H	mp. 170°C
76	B.2	5-methyl-2-thienyl	H	mp. 160°C
77	B.2	5-bromo-2-thienyl	H	mp. 192°C
78	B.2	5-cyano-2-thienyl	H	mp. 230°C
79	B.2	3-benzo[b]thienyl	H	mp. 151°C
80	B.17a	5-amino-2-thienyl	H	
81	B.17b		H	mp. 226°C
82	B.2	3-pyridinyl	H	mp. 165°C
83	B.2	2-furanyl	H	mp. 110°C
84	B.2	5-(2-thienyl)-2-thienyl	H	mp. 126°C
85	B.2		H	mp. 225°C

Table 3

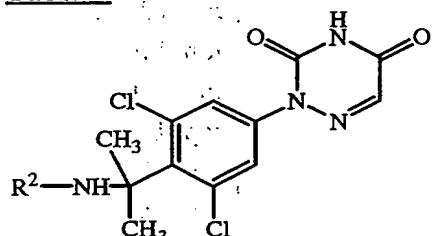


Co. No.	Ex. No.	R^{11a}	Salt / melting point
86	B.1a	2-fluorophenyl	
87	B.1a	2-methylphenyl	
88	B.1a	phenyl	
89	B.1a	2-chlorophenyl	
90	B.1a	3-fluorophenyl	
91	B.1a	3-methylphenyl	
92	B.1a	2-thienyl	
93	B.1a	3-chlorophenyl	
94	B.16b		HCl (1:3)

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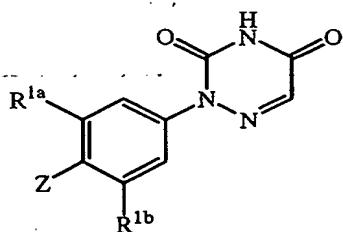
Co. No.	Ex. No.	R ^{1a}	Salt / melting point
95	B.16a	2-(bromomethyl)phenyl	
96	B.1a	4-fluorophenyl	
97	B.1a	4-pyridinyl	HCl (1:1)
98	B.1a	2-pyridinyl	

Table 4



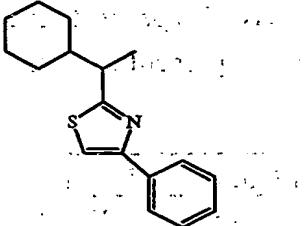
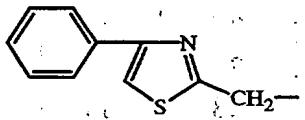
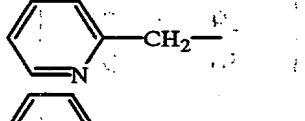
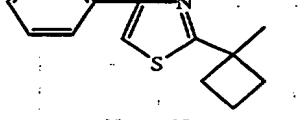
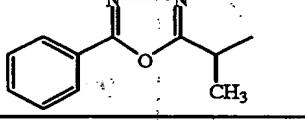
Co. No.	Ex. No.	R ²
99	B.12	NH ₂ -C(=S)-CH ₃
100	B.2	2-chloro-3-methyl-1,4-dihydro-2H-1,3-thiindole
101	B.13	(3-pyridinyl)-CO-

Table 5



Co. No.	Ex. No.	R ^{1a}	R ^{1b}	Z	Salt / melting point
102	B.1a	H	H		HCl (1:1); mp. 263.3°C
103	B.1a	Cl	Cl		mp. 177°C
104	B.1a	Cl	H		mp. 110°C

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Co. No.	Ex. No.	R ^{1a}	R ^{1b}	Z	Salt / melting point
105	B.2	Cl	H		mp. 216°C
106	B.1a	Cl	Cl		
107	B.1b	Cl	Cl		mp. 240°C
108	B.1a	Cl	Cl		ethanolate (1:1)
109	B.1a	Cl	Cl		

C. Pharmacological example

Example C.1 : *in vitro* inhibition of IL-5 production in human blood

Human whole blood stimulation

Peripheral blood from healthy male donors was drawn into heparinized syringes

(12.5 U heparin/ml). Blood samples were three-fold diluted in RPMI 1640 medium (Life Technologies, Belgium) supplemented with 2 mM L-glutamine, 100 U/ml penicillin and 100 µg/ml streptomycin, and 300 µl fractions were distributed in 24-well multidisc plates. Blood samples were preincubated (60 minutes at 37°C) in a humidified 6% CO₂-atmosphere with 100 µl of drug solvent (final concentration 0.02% dimethylsulfoxide in RPMI 1640) or with 100 µl of an appropriate dose of test compound before being stimulated by the addition of 100 µl of phytohemagglutinin HA17 (Murex, UK) at a final concentration of 2 µg/ml. After 48 hours, cell-free supernatant fluids were collected by centrifugation and stored at -70°C until tested for the presence of IL-5.

15 IL-5 measurements

IL-5 measurements were conducted as described in Van Wauwe et al. (1996, Inflamm Res, 45, 357-363) on page 358 using ELISA.

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Table 6 lists the percentage inhibition of IL-5 production (column "% inh") at a test dose of 1×10^{-6} M, or in case the percentage inhibition is marked with an "*" 1×10^{-5} M, for the compounds of the present invention.

Table 6

Co. No.	% inh.						
1	90.5	25	79	50	91	77	84
2	92	26	84	51	73	78	79
3	92	27	77	52	45	79	75
4	94	28	83	53	22	81	34
5	90	29	71	54	61	86	88
6	94	30	93	55	92	87	89
7	88	31	87	56	-4	88	94
8	85	32	91	57	85	89	84
9	88	33	90	58	84	90	91
10	85	34	93	59	82	91	81
11	88	35	63	60	28	92	80
12	70	36	9	61	29	93	84
13	75	37	92	62	53	96	82
14	78	38	93	63	38	97	90
15	81	39	72	64	86	100	15
16	57	40	89	65	36	101	19
17	94	42	26	66	53	102	8.5*
18	91	43	86	69	45	103	60
19	13	44	81	71	27	104	73
20	80	45	85	72	84	105	58.5
21	52	46	44	73	84	106	3
22	18	47	6	74	76	107	14
23	91	48	58	75	91	108	51
24	32	49	95	76	75	109	62

5 D. Composition examples

The following formulations exemplify typical pharmaceutical compositions suitable for systemic or topical administration to animal and human subjects in accordance with the present invention.

"Active ingredient" (A.I.) as used throughout these examples relates to a compound of

10 formula (I) or a pharmaceutically acceptable addition salt thereof.

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Example D.1 : film-coated tablets

Preparation of tablet core

A mixture of A.I. (100 g), lactose (570 g) and starch (200 g) was mixed well and thereafter humidified with a solution of sodium dodecyl sulfate (5 g) and polyvinyl-

5 pyrrolidone (10 g) in about 200 ml of water. The wet powder mixture was sieved, dried and sieved again. Then there was added microcrystalline cellulose (100 g) and hydrogenated vegetable oil (15 g). The whole was mixed well and compressed into tablets, giving 10.000 tablets, each comprising 10 mg of the active ingredient.

Coating

10 To a solution of methyl cellulose (10 g) in denatured ethanol (75 ml) there was added a solution of ethyl cellulose (5 g) in CH_2Cl_2 (150 ml). Then there were added CH_2Cl_2 (75 ml) and 1,2,3-propanetriol (2.5 ml). Polyethylene glycol (10 g) was molten and dissolved in dichloromethane (75 ml). The latter solution was added to the former and then there were added magnesium octadecanoate (2.5 g), polyvinyl-pyrrolidone (5 g) and concentrated
15 color suspension (30 ml) and the whole was homogenated. The tablet cores were coated with the thus obtained mixture in a coating apparatus.

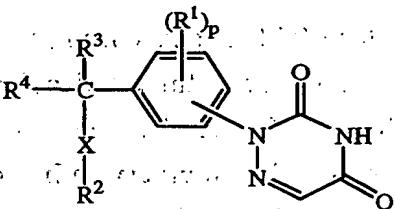
Example D.2 : 2% topical cream

To a solution of hydroxypropyl β -cyclodextrine (200 mg) in purified water is added A.I. (20 mg) while stirring. Hydrochloric acid is added until complete dissolution and

20 next sodium hydroxide is added until pH 6.0. While stirring, glycerol (50 mg) and polysorbate 60 (35 mg) are added and the mixture is heated to 70°C. The resulting mixture is added to a mixture of mineral oil (100 mg), stearyl alcohol (20 mg), cetyl alcohol (20 mg), glycerol monostearate (20 mg) and sorbate 60 (15 mg) having a temperature of 70°C while mixing slowly. After cooling down to below 25°C, the rest
25 of the purified water q.s. ad 1 g is added and the mixture is mixed to homogenous.

Claims

1. A compound having the formula



a *N*-oxide, a pharmaceutically acceptable addition salt or a stereochemically isomeric form thereof, wherein :

5 p represents an integer being 0, 1, 2, 3 or 4;

X represents O, S, NR⁵ or a direct bond;

Y represents O, S, NR⁵, or S(O)₂;

each R¹ independently represents C₁-6alkyl, halo, polyhaloC₁-6alkyl, hydroxy, mercapto, 10 C₁-6alkyloxy, C₁-6alkylthio, C₁-6alkylcarbonyloxy, aryl, cyano, nitro, Het³, R⁶, NR⁷R⁸ or C₁-4alkyl substituted with Het³, R⁶ or NR⁷R⁸;

R² represents Het¹, C₃-7cycloalkyl, C₁-6alkyl or C₁-6alkyl substituted with one or two substituents selected from hydroxy, cyano, amino, mono- or di(C₁-4alkyl)amino, 15 C₁-6alkyloxy, C₁-6alkylsulfonyloxy, C₁-6alkyloxycarbonyl, C₃-7cycloalkyl, aryl, aryloxy, arylthio, Het¹, Het¹oxy and Het¹thio; and if X is O, S or NR⁵, then R² may also represent aminocarbonyl, aminothiocarbonyl, C₁-4alkylcarbonyl, C₁-4alkylthiocarbonyl, arylcarbonyl, arylthiocarbonyl, Het¹carbonyl or Het¹thiocarbonyl;

R³ represents hydrogen, C₁-6alkyl or C₃-7cycloalkyl;

20 R⁴ represents hydrogen, C₁-6alkyl or C₃-7cycloalkyl; or

R³ and R⁴ taken together form a C₂-6alkanediyl;

R⁵ represents hydrogen or C₁-4alkyl;

each R⁶ independently represents C₁-6alkylsulfonyl, aminosulfonyl, mono- or di-(C₁-4alkyl)aminosulfonyl, mono- or di(benzyl)aminosulfonyl, polyhaloC₁-6alkylsulfonyl, 25 C₁-6alkylsulfinyl, phenylC₁-4alkylsulfonyl, piperazinylsulfonyl, aminopiperidinylsulfonyl, piperidinylaminosulfonyl, N-C₁-4alkyl-N-piperidinylaminosulfonyl or mono- or di(C₁-4alkyl)aminoC₁-4alkylsulfonyl;

each R⁷ and each R⁸ are independently selected from hydrogen, C₁-4alkyl, hydroxy-C₁-4alkyl, dihydroxyC₁-4alkyl, aryl, arylC₁-4alkyl, C₁-4alkyloxyC₁-4alkyl, C₁-4alkylcarbonyl, aminocarbonyl, arylcarbonyl, Het³carbonyl, C₁-4alkylcarbonyloxyC₁-4alkylcarbonyl, hydroxyC₁-4alkylcarbonyl, C₁-4alkyloxycarbonylcarbonyl, mono- or di(C₁-4alkyl)aminoC₁-4alkyl, arylaminocarbonyl, arylaminothiocarbonyl, Het³aminocarbonyl, Het³aminothiocarbonyl, C₃-7cycloalkyl, pyridinylC₁-4alkyl,

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C_{1-4} alkanediyl-C(=O)-O-R¹⁴, -C(=O)-O-R¹⁴, -Y-C₁₋₄alkanediyl-C(=O)-O-R¹⁴, Het³ and R⁶;

R⁹ and R¹⁰ are each independently selected from hydrogen, C₁₋₄alkyl, hydroxyC₁₋₄alkyl, dihydroxyC₁₋₄alkyl, phenyl, phenylC₁₋₄alkyl, C₁₋₄alkyloxyC₁₋₄alkyl, C₁₋₄alkylcarbonyl, aminocarbonyl, phenylcarbonyl, Het³carbonyl, C₁₋₄alkylcarbonyloxyC₁₋₄alkylcarbonyl, hydroxyC₁₋₄alkylcarbonyl, C₁₋₄alkyloxycarbonylcarbonyl, mono- or di(C₁₋₄alkyl)aminoC₁₋₄alkyl, phenylaminocarbonyl, phenylaminothiocarbonyl, Het³aminocarbonyl, Het³aminothiocarbonyl, C₃₋₇cycloalkyl, pyridinylC₁₋₄alkyl, C₁₋₄alkanediyl-C(=O)-O-R¹⁴, -C(=O)-O-R¹⁴, -Y-C₁₋₄alkanediyl-C(=O)-O-R¹⁴, Het³ and R⁶;

each R¹¹ independently being selected from hydroxy, mercapto, cyano, nitro, halo, trihalomethyl, C₁₋₄alkyloxy, formyl, trihaloC₁₋₄alkylsulfonyloxy, R⁶, NR⁷R⁸, C(=O)NR⁷R⁸, -C(=O)-O-R¹⁴, -Y-C₁₋₄alkanediyl-C(=O)-O-R¹⁴, aryl, aryloxy, arylcarbonyl, C₃₋₇cycloalkyl, C₃₋₇cycloalkyloxy, phthalimide-2-yl, Het³, Het⁴ and C(=O)Het³;

R¹² and R¹³ are each independently selected from hydrogen, C₁₋₄alkyl, hydroxyC₁₋₄alkyl, dihydroxyC₁₋₄alkyl, phenyl, phenylC₁₋₄alkyl, C₁₋₄alkyloxyC₁₋₄alkyl, C₁₋₄alkylcarbonyl, phenylcarbonyl, C₁₋₄alkylcarbonyloxyC₁₋₄alkylcarbonyl, hydroxyC₁₋₄alkylcarbonyl, C₁₋₄alkyloxycarbonylcarbonyl, mono- or di(C₁₋₄alkyl)aminoC₁₋₄alkyl, phenylaminocarbonyl, phenylaminothiocarbonyl, C₃₋₇cycloalkyl, pyridinylC₁₋₄alkyl, C₁₋₄alkanediyl-C(=O)-O-R¹⁴, -C(=O)-O-R¹⁴, -Y-C₁₋₄alkanediyl-C(=O)-O-R¹⁴ and R⁶;

each R¹⁴ independently represents hydrogen, C₁₋₄alkyl, C₃₋₇cycloalkyl, aminocarbonylmethylene or mono- or di(C₁₋₄alkyl)aminocarbonylmethylene; aryl represents phenyl optionally substituted with one, two or three substituents each independently selected from nitro, azido, cyano, halo, hydroxy, C₁₋₄alkyl, C₃₋₇cycloalkyl, C₁₋₄alkyloxy, formyl, polyhaloC₁₋₄alkyl, NR⁹R¹⁰, C(=O)NR⁹R¹⁰, C(=O)-O-R¹⁴, R⁶, -O-R⁶, phenyl, Het³, C(=O)Het³ and C₁₋₄alkyl substituted with hydroxy, C₁₋₄alkyloxy, C(=O)-O-R¹⁴, -Y-C₁₋₄alkanediyl-C(=O)-O-R¹⁴, Het³ or NR⁹R¹⁰;

Het¹ represents a heterocycle selected from pyrrolyl, pyrrolinyl, imidazolyl, imidazolinyl, pyrazolyl, pyrazolinyl, triazolyl, tetrazolyl, furanyl, tetrahydrofuranyl, thienyl, thiolanyl, dioxolanyl, oxazolyl, oxazolinyl, isoxazolyl, thiazolyl, thiazolinyl, isothiazolyl, thiadiazolyl, oxadiazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyranyl, pyridazinyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl, dioxanyl, dithianyl, trithianyl, triazinyl, benzothienyl, isobenzothienyl, benzofuranyl, isobenzofuranyl, benzothiazolyl, benzoxazolyl, indolyl, isoindolyl, indolinyl, purinyl, 1*H*-pyrazolo[3,4-d]pyrimidinyl, benzimidazolyl, quinolyl, isoquinolyl, cinnolinyl, phtalazinyl,

quinazolinyl, quinoxalanyl, thiazolopyridinyl, oxazolopyridinyl and imidazo[2,1-b]thiazolyl; wherein said heterocycles each independently may optionally be substituted with one, or where possible, two or three substituents each independently selected from Het², R¹¹ and C₁₋₄alkyl optionally substituted with one or two substituents

5 independently selected from Het² and R¹¹;

Het² represents a heterocycle selected from pyrrolyl, pyrrolinyl, imidazolyl, imidazolinyl, pyrazolyl, pyrazolinyl, triazolyl, tetrazolyl, furanyl, tetrahydrofuranyl, thienyl, thiolanyl, dioxolanyl, oxazolyl, oxazolinyl, isoxazolyl, thiazolyl, thiazolinyl, isothiazolyl, thiadiazolyl, oxadiazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyranyl, pyridazinyl, dioxanyl, dithianyl, trithianyl, triazinyl, benzothienyl, isobenzothienyl, benzofuranyl, isobenzofuranyl, benzothiazolyl, benzoxazolyl, indolyl, isoindolyl, indolinyl, purinyl, 1*H*-pyrazolo[3,4-d]pyrimidinyl, benzimidazolyl, quinolyl, isoquinolyl, cinnolinyl, phthalazinyl, quinazolinyl, quinoxalanyl, thiazolopyridinyl, oxazolopyridinyl and imidazo[2,1-b]thiazolyl; wherein said heterocycles each independently may optionally be substituted with one, or where possible, two or three substituents each

10 independently selected from R¹¹ and C₁₋₄alkyl optionally substituted with one or two substituents independently selected from R¹¹.

15 Het³ represents a monocyclic heterocycle selected from pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl and tetrahydropyranyl; wherein said monocyclic heterocycles each independently may optionally be substituted with, where possible, one, two, three or four substituents each independently selected from hydroxy, C₁₋₄alkyl, C₁₋₄alkyloxy, C₁₋₄alkylcarbonyl, piperidinyl, NR¹²R¹³, C(=O)-O-R¹⁴, R⁶ and C₁₋₄alkyl substituted with one or two substituents independently selected from hydroxy, C₁₋₄alkyloxy, phenyl, C(=O)-O-R¹⁴, -Y-C₁₋₄alkanediyl-C(=O)-O-R¹⁴, R⁶ and NR¹²R¹³;

20 Het⁴ represents a monocyclic heterocycle selected from pyrrolyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl, furanyl, thienyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, thiadiazolyl, oxadiazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyranyl, pyridazinyl and triazinyl.

25 30 2. A compound as claimed in claim 1 wherein the 6-azauracil moiety is in the para position relative to the carbon atom bearing the -X-R², R³ and R⁴ substituents.

35 3. A compound as claimed in claims 1 or 2 wherein R² is a monocyclic heterocycle selected from pyrrolyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl, furanyl, thienyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, thiadiazolyl, oxadiazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyranyl, pyridazinyl and triazinyl, wherein said monocyclic heterocycles each independently may optionally be substituted with one, or where

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possible, two or three substituents each independently selected from Het², R¹¹ and C₁₋₄alkyl optionally substituted with Het² or R¹¹.

4. A compound as claimed in any one of claims 1 to 3 wherein R³ and R⁴ are both 5 methyl and -X-R² is Het¹.

5. A compound as claimed in any one of claims 1 to 4 wherein p is 1 or 2 and each R¹ is chloro.

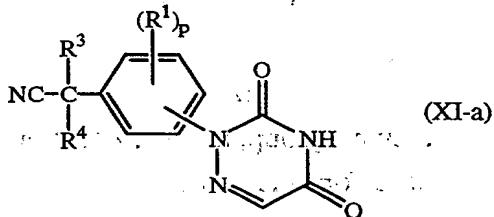
10 6. A composition comprising a pharmaceutically acceptable carrier and, as active ingredient, a therapeutically effective amount of a compound as claimed in any one of claims 1 to 5.

15 7. A process for preparing a composition as claimed in claim 6, , wherein a pharmaceutically acceptable carrier is intimately mixed with a therapeutically effective amount of a compound as defined in any one of claims 1 to 5.

8. A compound as claimed in any one of claims 1 to 5 for use as a medicine.

20 9. Use of a compound as claimed in any one of claims 1 to 5 in the manufacture of a medicament for treating eosinophil-dependent inflammatory diseases.

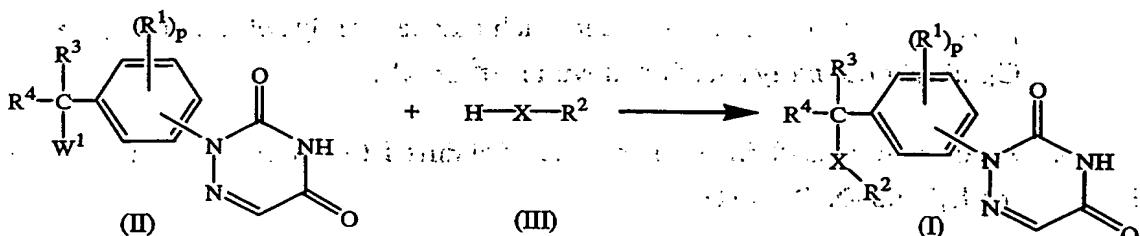
10. A compound of formula



25 wherein R¹, R³, R⁴ and p are as defined in claim 1.

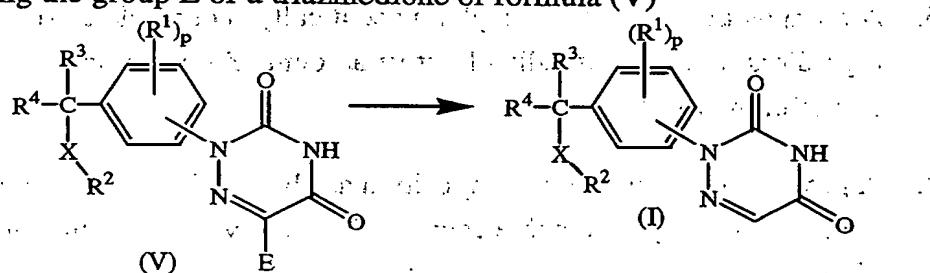
11. A process for preparing a compound as claimed in claim 1, characterized by,
 a) reacting an intermediate of formula (II) wherein W¹ is a suitable leaving group with an appropriate reagent of formula (III) optionally in a reaction-inert solvent and 30 optionally in the presence of a base at a temperature ranging between - 70°C and reflux temperature;

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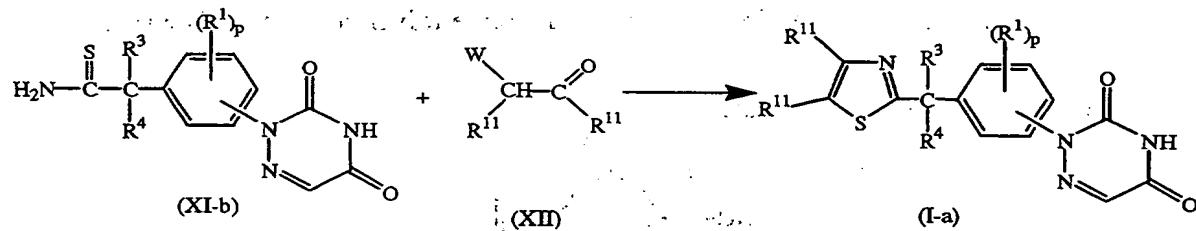
wherein R^2 , R^3 , R^4 , p and X are as defined in claim 1;

b) eliminating the group E of a triazinedione of formula (V)



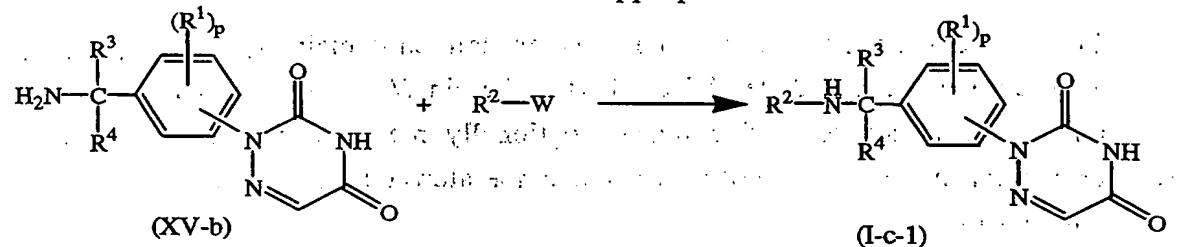
5 wherein E is an appropriate electron attracting group and R¹, R², R⁴, X and p are as defined in claim 1;

c) cyclizing a thioamide of formula (XI-b) with an intermediate of formula (XII) in a suitable solvent



10 wherein W is a suitable leaving group, and R¹, R³, R⁴ and p are as defined in claim 1; thus forming a compound of formula (I-a);

d) reacting an amine derivative of formula (XV-b) with an intermediate of formula R^2-W or with a functional derivative thereof in an appropriate solvent



15 wherein W is a suitable leaving group and R¹, R², R³, R⁴ and p are as defined in claim 1; and, if desired, converting compounds of formula (I) into each other following art-known transformations, and further, if desired, converting the compounds of formula

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(I), into a therapeutically active non-toxic acid addition salt by treatment with an acid, or into a therapeutically active non-toxic base addition salt by treatment with a base, or conversely, converting the acid addition salt form into the free base by treatment with alkali, or converting the base addition salt into the free acid by treatment with acid; and
5 also, if desired, preparing stereochemically isomeric forms or *N*-oxide forms thereof.

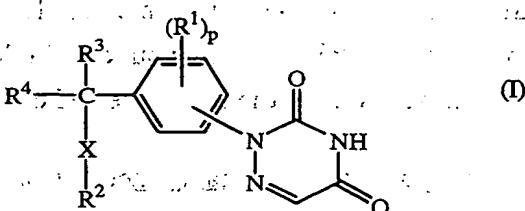
12. A process of marking a receptor comprising the steps of
 - a) radiolabelling a compound as defined in claim 1;
 - b) administering said radiolabelled compound to biological material,
 - 10 c) detecting the emissions from the radiolabelled compound.
13. A process of imaging an organ, characterized by, administering a sufficient amount of a radiolabelled compound of formula (I) in an appropriate composition, and detecting the emissions from the radioactive compound.

ABSTRACT

5

NOVEL IL-5 INHIBITING 6-AZAUURACIL DERIVATIVES

The present invention is concerned with the compounds of formula



the *N*-oxides, the pharmaceutically acceptable addition salts and the stereochemically isomeric forms thereof, wherein *p* is 0 to 4; *X* is O, S, NR⁵ or a direct bond; *Y* is O, S, NR⁵ or S(O)₂; *R*¹ independently is C₁₋₆alkyl, halo, polyhaloC₁₋₆alkyl, hydroxy, mercapto, C₁₋₆alkyloxy, C₁₋₆alkylthio, C₁₋₆alkylcarbonyloxy, aryl, cyano, nitro, Het³, R⁶, NR⁷R⁸ or substituted C₁₋₄alkyl; *R*² is Het¹, C₃₋₇cycloalkyl or optionally substituted C₁₋₆alkyl and if *X* is O, S or NR⁵, then *R*² may also represent aminocarbonyl, aminothiocarbonyl, C₁₋₄alkylcarbonyl, C₁₋₄alkylthiocarbonyl, arylcarbonyl, arylthiocarbonyl, Het¹carbonyl or Het¹thiocarbonyl; *R*³ and *R*⁴ independently are hydrogen, C₁₋₆alkyl or C₃₋₇cycloalkyl; *R*⁵ and *R*⁴ form a C₂₋₆alkanediyl; *R*⁵ is hydrogen or C₁₋₄alkyl; *R*⁶ is a sulfonyl or sulfinyl derivative; *R*⁷ and *R*⁸ are independently hydrogen, optionally substituted C₁₋₄alkyl, aryl, a carbonyl containing moiety, C₃₋₇cycloalkyl, -Y-C₁₋₄alkanediyl-C(=O)-O-R¹⁴, Het³ and R⁶; *R*¹¹ is hydroxy, mercapto, cyano, nitro, halo, trihalomethyl, C₁₋₄alkyloxy, formyl, trihaloC₁₋₄alkylsulfonyloxy, R⁶, NR⁷R⁸, C(=O)NR⁷R⁸, C₁₋₄alkanediyl-C(=O)-O-R¹⁴, -C(=O)-O-R¹⁴, -Y-C₁₋₄alkanediyl-C(=O)-O-R¹⁴, aryl, aryloxy, arylcarbonyl, C₃₋₇cycloalkyl, C₃₋₇cycloalkyloxy, phthalimide-2-yl, Het³, Het⁴ and C(=O)Het³; *R*¹⁴ is hydrogen, C₁₋₄alkyl, C₃₋₇cycloalkyl, aminocarbonylmethylene or mono- or di(C₁₋₄alkyl)aminocarbonylmethylene; aryl is optionally substituted phenyl; Het¹, Het², Het³ and Het⁴ are optionally substituted heterocycles; to processes for their preparation and compositions comprising them. It further relates to their use as a medicine.

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